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Corticosteroids for pulmonary sarcoidosis (Review)

Paramothayan NS, Lasserson TJ, Jones P

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TABLE OF CONTENTS

[Intervention Review]

Corticosteroids for pulmonary sarcoidosis

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ABSTRACT

Background

Pulmonary sarcoidosis is a common condition with an unpredictable course. Oral (OCS) or inhaled steroids (ICS) are widely used in its treatment, but there is no consensus about when and in whom therapy should be initiated, what dose should be given and for how long. Corticosteroids given for several months have deleterious side-effects so it is important to know whether they have any maintained benefit in pulmonary sarcoidosis.

Objectives

To determine the randomised controlled trial (RCT) evidence for the benefit of corticosteroids (oral or inhaled) in the treatment of pulmonary sarcoidosis.

Search methods

CENTRAL, MEDLINE, and EMBASE were searched using predefined terms. Bibliographies of retrieved RCTs and reviews were searched for additional RCTs. Pharmaceutical companies and authors of identified RCTs were contacted for other published and unpublished studies. Searches are current as of May 2008.

Selection criteria

Two reviewers independently assessed full text articles for inclusion based upon the following criteria: the study had to be a RCT or controlled clinical trial in adults with histological evidence of pulmonary sarcoidosis, treated with OCS (oral steroids) or ICS (oral steroids), compared with a control.

Data collection and analysis

Study quality was assessed and data extracted independently by two reviewers. The primary outcome was CXR (chest x-ray). Outcomes were analysed as continuous and dichotomous outcomes, using standard statistical techniques. Heterogeneity was explored where it was identified.

Main results

Thirteen RCTs of variable quality involving 1066 participants met the inclusion criteria of the review. The oral steroid dose was equivalent to prednisolone 4-40 mg/day. OCS: there was an improvement in CXR over 3-24 months (Relative Risk (RR): 1.46 [1.01 to 2.09], 3 studies), but this finding requires cautious interpretation. No other significant differences were identified on secondary outcomes. ICS: Data were inadequate to perform meaningful analysis of data on CXR. Two studies showed no improvement in lung function, In one study there was an improvement in diffusing capacity in the treated group. There were no data on side-effects. In one study symptoms improved at the end of six months of treatment.

Authors' conclusions

Oral steroids improved the chest X-ray and a global score of CXR, symptoms and spirometry over 3-24 months. However, there is little evidence of an improvement in lung function. There are limited data beyond two years to indicate whether oral steroids have any modifying effect on long-term disease progression. Oral steroids may be of benefit for patients with Stage 2 and 3 disease with moderate to severe or progressive symptoms or CXR changes.

PLAIN LANGUAGE SUMMARY

Corticosteroids for pulmonary sarcoidosis

Sarcoidosis is a common disease that can affect several parts of the body. The cause of the disease is unknown, and it often gets better without treatment. Sarcoidosis is more likely among some ethnic groups (including African-Americans and African-Caribbeans), for whom the disease has worse outcomes. When sarcoidosis affects the lungs, it can cause breathlessness, coughs, and lung problems, and lead to more complications and death. The review of trials found that using corticosteroids for lung sarcoidosis leads to some short-term benefit in terms of chest x-ray, but there is limited evidence that this benefit lasts or affects the long term outcomes of the disease.

BACKGROUND

Sarcoidosis is a common, multi system granulomatous disorder. Lungs are frequently involved and can often progress to pulmonary fibrosis. This results in increased morbidity and mortality. Certain ethnic groups, including the Black American and Afro-Caribbean populations have a higher incidence of pulmonary sarcoidosis, which runs a particularly relentless course with higher morbidity and mortality. The severity of lung involvement is assessed on the basis of the patient's symptoms (particularly dyspnoea and cough), on changes on the chest x-ray (which are staged from 1-4) and on deteriorating lung function tests.

Spontaneous resolution can occur without treatment. Patients with evidence of worsening symptoms or lung function are treated with high doses of oral corticosteroids with the objective of preventing disease progression and to alleviate symptoms. Patients with extra pulmonary sarcoidosis, such as neurosarcoidosis, hypercalcaemia and uveitis are often treated with corticosteroids but they are not considered in this review. There is no consensus about when corticosteroid therapy should be initiated, what dose of corticosteroids should be given and for how long. Corticosteroids given in high doses for several months have deleterious side effects so it is important to know whether they have any beneficial effect in pulmonary sarcoidosis.

OBJECTIVES

The objective of the review was to determine the evidence derived from RCTs for the efficacy of corticosteroids (oral or inhaled) in the treatment of patients with pulmonary sarcoidosis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials and controlled clinical trials with standardised non-corticosteroid interventions were included.

Types of participants

Adult patients with histological evidence of pulmonary sarcoidosis were included. Evidence of radiographic changes and deterioration in lung function was also used as an inclusion criterion in the primary trials. Studies that included patients with other types of interstitial lung disease were excluded.

Types of interventions

Oral or inhaled corticosteroids, administered for more than two months. The control group had to have received placebo or no treatment. Interventions involving other drugs for the treatment of pulmonary sarcoidosis were excluded.

Participants had been previously treated with steroids (any type, dose or route) were excluded. For studies where some participants had not previously received steroid treatment, data were only extracted and entered for participants who were steroid-naive at outset, where this was available.

For the update the initial inclusion criteria were clarified. One study assessing inhaled steroids as an oral steroid sparing agent was also included.

Types of outcome measures

Primary outcomes

Changes on chest x-ray (CXR) using standardised radiographic scores.

Lung function measurements:

1. Forced Expiratory Volume in one second (FEV_1)
2. Forced Vital Capacity (FVC)
3. Inspiratory Vital Capacity (IVC)
4. Diffusing capacity - DLCO and DLCO/Va; single breath diffusing capacity of carbon monoxide (TLco)

Secondary outcomes

Symptom scores

Adverse events

Search methods for identification of studies

Electronic searches

Searches were carried out on CENTRAL, MEDLINE, and EMBASE using predefined terms. Please see Appendix 1 and Appendix 2 for the search strategies used for the individual databases.

Searches are current to May 2008.

Searching other resources

Bibliographies of each retrieved RCT and review were searched for additional papers that may contain RCTs. Pharmaceutical companies were contacted for additional trial data where possible. Authors of identified RCTs were contacted for other published and unpublished studies. All trials were included, irrespective of language.

Data collection and analysis

Selection of studies

Each article identified was reviewed by the reviewer to see if it met the inclusion criteria. When there was doubt, a second reviewer assessed the article and a consensus was reached.

All trials were entered and scored using the following principles:

Two reviewers independently assessed the quality of the full text version of all included papers using the Cochrane system. Study quality was assessed according to the following variables:

Data extraction and management

Data for the trial was extracted by one of the reviewers and sent to the authors for verification. For those studies where verification could not be obtained, a second independent reviewer was used.

Assessment of risk of bias in included studies

(1) CONCEALMENT OF ALLOCATION
A: ADEQUATE - if there was concealed allocation of participants to treatment or control; i.e. a central allocation scheme where study investigators can have no knowledge as to which treatment has been given to which participant, such as by external person or use of coded containers/envelopes.

B: UNCLEAR - it is not reported/information unavailable as to how treatment was allocated.
C: INADEQUATE - if there was alternate allocation, reference to case record number, date of birth, day of the week, or an open test or random numbers.

(2) BLINDING OF INTERVENTIONS: where both the investigators and the patient were not aware whether they were receiving the active drug or the placebo.

(3) WITHDRAWALS / DROPOUTS: it was noted whether all randomised subjects were accounted for in the results and the reason for this was also noted (e.g.. due to side effects of drugs).

(4) BLINDING OF OUTCOME ASSESSMENT: it was noted whether the study outcomes were assessed by a person who was blinded to the treatment allocation and whether more the one person assessed subjective results such as changes in CXR.
Inter - rater reliability was measured using simple agreement.

The methodological quality of each trial was assessed using a 0-5 scale based upon the method described by Jadad 1996 and summarised as follows:
(1) Was the study described as randomised (1= yes; 0= no)?
(2) Was the study described as being double blind (1= yes; 0= no)?
(3) Was there a description of withdrawals and dropouts (1= yes; 0= no)?
(4) Was the method of randomisation well described and appropriate (1= yes; 0= no)?
(5) Was the method of double blinding well described and appropriate (1= yes; 0= no)?
(6) Deduct 1 point if methods for randomisation or blinding were inappropriate.

In addition each study was assessed for the reliability of the diagnosis of sarcoidosis using pre-specified criteria agreed between the reviewers.

Assessment of heterogeneity

Studies were combined using Fixed Effect modelling. Tests for heterogeneity were carried out using the I^2 statistic, which measures the amount of inconsistency between studies which is not attributable to chance. The greater the I^2 percentage, the greater the amount of inconsistency there is between studies.

Data synthesis

Continuous variables

Data were combined using RevMan analyses. For outcomes reported on the same metrics, data were combined using a weighted mean difference (WMD). For outcomes reporting the same measurements but on different metrics, a standardised mean difference was employed (SMD).

Dichotomous variables

Dichotomous data were combined using a Relative Risk (RR). A similar approach was used for other data that was reported in categories: "improved", "unchanged" or "worse". The distribution of these categorical responses between treatment and control can be compared statistically, but such tests are not yet available in the Cochrane software.

To display the results graphically, and test whether the effects of steroid and placebo were different, each category of CXR change was analysed separately, comparing the proportion of steroid treated and placebo treated patients within that category. (Note: any difference in the proportion of unchanged patients treated with steroids or placebo requires careful interpretation, since it will be influenced by the numbers of patients improved as well as worse. This category of response is best ignored, the graphs are retained within the review for completeness).

Subgroup analysis and investigation of heterogeneity

The only planned sub-group analysis possible was by radiographic stage of disease.

Sensitivity analysis

Where the I^2 result measures approximately the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error. Where this indicates significant inconsistency across the studies Random Effects modelling was used in order to determine whether the direction and magnitude of the effect estimate was altered when compared with the Fixed Effect model.

RESULTS

Description of studies

Results of the search

For a history of search results see Table 1. From a total of 2757 citations retrieved from electronic literature searches (all years to May 2008), we have included 13 studies (23 references), and excluded 16 studies (16 references).

Included studies

Thirteen studies met the inclusion criteria.

For a full description of each study, see Characteristics of included studies.

Design

All studies were randomised. Methods of randomisation were reported in three studies (Alberts 1995; Israel 1973; Selroos 1979). All studies were described as double-blind with the exception of Selroos 1979 and Roth 1975 in which steroids were compared with no treatment. Roth 1975 recruited participants on an open-ended basis over a period of ten years.

Participants

A total of 1066 participants were recruited in the studies. Median sample size was 45 (range: 15 to 280). All were adults with pulmonary sarcoidosis. The majority of participants in the studies were male Caucasians. The participants varied in terms of the duration of the disease. Baughman 2002; du Bois 2003 and Erkkila 1988 recruited participants with newly detected sarcoidosis. Please see Table of Included Studies for details of exclusion criteria for each study.

Diagnosis of sarcoidosis was based upon CXR in all studies apart from Selroos 1979. Histology confirmed a diagnosis of sarcoidosis in all studies.

CXR staging of participants varied between the studies. Participants with stages 1-3 were recruited to Alberts 1995; Israel 1973; Zaki 1987 and Ludwig 2005. Baughman 2002 recruited participants with CXR staging 1-4 and McGrath 2002 recruited participants from stages 2 to 4. du Bois 2003; Erkkila 1988; Roth 1975 and Pietinalho 1999 recruited participants from stages 1-2, and Selroos 1979 recruited participants exclusively from stage 2. James 1967 recruited participants with multisystem disorders.

Some participants had prior treatment with OCS in du Bois 2003 and Milman 1994. All other participants in the remaining studies were steroid-naive at outset.

See Characteristics of included studies for baseline lung functions, age, gender and ethnicity for each study.

Interventions

There were four comparisons that fell within the scope of the review. OCS versus placebo (Israel 1973; James 1967; Pietinalho 1999; Zaki 1987); OCS versus no treatment (Roth 1975; Selroos 1979); ICS versus placebo (Alberts 1995; du Bois 2003; Erkkila 1988; Ludwig 2005; McGrath 2002; Milman 1994) and ICS versus placebo an OCS-sparing agent (Baughman 2002). Pietinalho 1999 compared inhaled steroid treatment with placebo control subsequent to oral steroid versus placebo treatment. Participants randomised to OCS received ICS and those randomised to oral placebo received inhaled placebo. Data were only pooled for the first treatment period (OCS versus placebo).

OCS dosage varied between the studies (4 mg administered to some participants in Selroos 1979; and 40 mg prednisolone given to participants in Roth 1975 and Zaki 1987).

ICS type and dose varied between the studies. Alberts 1995 and Milman 1994 used budesonide (BUD) at 1200 mcg per day. Erkkila 1988 and McGrath 2002 also compared BUD with placebo but at 800 mcg and 1600 mcg per day respectively. Baughman 2002 and du Bois 2003 compared fluticasone (FP) with placebo at 880 mg and 2000 mg per day respectively, and Ludwig 2005 compared HFA-BDP 800mcg per day with placebo.

Treatment duration varied greatly between the studies, from eight weeks (Erkkila 1988) to two years (Zaki 1987). Due to the nature of sarcoidosis long-term outcome assessment is crucial in determining whether short-term treatment leads to benefit in the long-term. Follow-up was conducted in seven studies (Alberts 1995; Israel 1973; McGrath 2002; Pietinalho 1999; Roth 1975; Selroos 1979; Zaki 1987). No data could be used from these studies in a meta-analysis. Length of follow-up varied within some studies ranging from 3 to 14 years in Roth 1975, and one to 11 years (Israel 1973).

Outcome measures

The primary endpoints varied across the studies. With the exception Baughman 2002 the studies reported data on CXR. All studies reported data on lung function.

All the authors of these identified RCTs were contacted twice by e-mail or post for any additional information as well as for details of the randomisation procedure, concealment and blinding and details about withdrawals and dropouts.

Risk of bias in included studies

For each study, Jadad scores/Cochrane allocation concealment grades were assessed by three different people and were as follows:
Alberts 1995 (4/A); Baughman 2002 (3/B); du Bois 2003 (3/B); Erkkila 1988 (3/B); James 1967 (4/A); Israel 1973 (3/B); Ludwig 2005 (5/B); McGrath 2002 (3/B); Milman 1994 (3/B); Roth 1975 (1/B); Selroos 1979 (1/B); Zaki 1987 (3/B).

Although there was some variation between the Jadad scores, this tends to reflect differences in the quality of reporting rather than differences in terms of methodological quality.

Studies were of variable quality. Although they were all described as randomised, verification of the randomisation procedure was available for Israel 1973; Selroos 1979 and Ludwig 2005. In two studies (Roth 1975; Selroos 1979) there was no placebo control and in the absence of adequate blinding, this may have distorted any treatment effect.

The primary outcome was reported in all studies with the exception of Baughman 2002. Subjective measurements of symptoms were not widely reported across the studies. Participants suffering from all stages of sarcoidosis were recruited and long-term outcome assessment was carried out in seven studies.

Effects of interventions

Two studies which had been excluded previously because over concerns over the data and randomisation were deemed to have met the inclusion criteria (Roth 1975; Milman 1994).

Results from the meta-analyses are reported by comparisons and then outcome (CXR changes, symptoms and lung function) at the end of treatment with oral steroids or with inhaled steroids. The follow-up data were not analysed but some of the results of the follow-up studies have been included for discussion.

Oral steroids versus control

Data were pooled separately for placebo and no treatment controlled trials.

CXR (Israel 1973; James 1967; Selroos 1979; Zaki 1987; Pietinalho 1999)

Combining the three placebo-controlled studies resulted in moderate to high inconsistency between the studies (James 1967; Pietinalho 1999 and Zaki 1987; I^2: 67.1%). Fixed Effect and Random Effects models resulted in a significant benefit in steroid-treated participants (RR (FE): 1.42 [95%CI: 1.20 to 1.69]; (RE) 1.46 [1.01 to 2.09]). The duration of treatment varies considerably between the studies (3 to 24 months) and may account for differences in response. The RE estimate is marginally clear the line of no difference and should be treated with caution, although this does not preclude the possibility of clinically meaningful benefit for short-term outcome. The proportion of patients in the steroid group who deteriorated was significantly lower than in the placebo group (RR 0.39 [95% CI: 0.18 to 0.87]).

Selroos 1979 reported changes in CXR at seven, 24 and 48 months of treatment. By seven months there was a statistically significant difference in favour of the treated versus the untreated groups in terms of the number of participants with normal or improved CXR

(treated group: 17/19 versus untreated: 11/18, P<0.05). By 24 and 48 months the difference is no longer significant (24 months: treated group: 12/19 versus untreated group: 10/13; 48 months: treated group: 11/13 versus untreated group: 9/12, no P values reported).

Israel 1973 recorded CXR changes, lung function and symptoms in 83 patients. These outcomes were grouped together as a global outcome in an unspecified manner. There was an improvement in global outcome at the end of treatment compared to the placebo group. Sub-group analysis of the data showed an improvement in this global score in patients with radiographic stage 2 and 3 disease but not with stage 1 disease. There was no significant difference between the treated and control groups with regard to the number of patients, who on global assessment, remained unchanged or deteriorated.

Lung function (Pietinalho 1999; Selroos 1979; Zaki 1987)

The results of lung function data from the different studies could not be combined.

Zaki 1987 measured FEV_1, FVC and DLCO (as dichotomous data) in 159 patients after treatment with oral steroids for two years. There was no significant difference between the treated and control groups in any of these outcomes. Sub-group analysis of the different radiographic stages did not reveal any differences between the treated and control groups.

Selroos 1979 and Pietinalho 1999 measured FVC and DLCO as continuous data. There were no statistically significant differences detected in the Pietinalho 1999 study for participants with stage 1 disease at baseline for either FVC or DLCO. For participants with stage 2 disease at baseline the difference between steroid and placebo treatment for FVC and DLCO were not statistically significant at three months (FVC: steroid group: 93.3% (SD 11.8) versus placebo group 87.3% (SD 11.9); DLCO: steroid group: 97.1% (SD 18.1) versus placebo group: 92.5% (SD 18)).

Symptoms

None of the studies reported discreet data on symptom assessment at any time point.

Inhaled steroids versus placebo

CXR (Alberts 1995; du Bois 2003; Erkkila 1988; McGrath 2002; Milman 1994; Pietinalho 1999)

Data could not be pooled from the du Bois 2003; Milman 1994 and Pietinalho 1999, as data were presented for all participants regardless of whether participants had been treated with oral steroids prior to study entry or not.

The CXR results from Alberts 1995 could not be analysed as the numbers given in the paper did not add up correctly, and verification of data could not be obtained.

Data were pooled for three small studies (Erkkila 1988; McGrath 2002; Ludwig 2005). There were no significant differences between ICS and placebo treatment (CXR improved: RR 0.8 [95% CI: 0.39 to 1.62]; CXR unchanged: RR 1.17 [95%CI: 0.73 to 1.88]; CXR deteriorated: RR: 1.15 [95%CI: 0.31 to 4.27]).

Lung function (Alberts 1995; du Bois 2003; Erkkila 1988; McGrath 2002; Milman 1994; Pietinalho 1999)

Data could not be pooled from the du Bois 2003; Milman 1994 and Pietinalho 1999, as data were presented for all participants and not according to whether participants had been treated with oral steroids prior to study entry or not.

Data were pooled from three small studies (Alberts 1995; McGrath 2002) for FEV_1 (% predicted) and DLCO (% predicted). No statistically significant differences were observed for either outcome (FEV_1: 1.61% [95% CI: -4.94 to 8.16]; DLCO: -2.48% [05%CI: -11.18 to 6.28]).

Alberts 1995 measured IVC (%) and Ludwig 2005 measured IVC as litres. Neither study reported a significant difference.

Erkkila 1988 measured DLCO/Va (as dichotomous data) in 19 patients at the end of treatment with inhaled steroids for 8 -10 weeks. They dichotomized their data in terms of improved or not improved using +15% as the criterion for improvement. There were more patients in the control group in whom DLCOL/Va was unchanged but there was no difference between treated and control groups in deterioration of DLCO/Va.

Alberts 1995 showed an improvement in their global clinical index (that included patients' symptoms) in the treated group.

Symptoms (du Bois 2003; Milman 1994)

No data were presented separately for participants who had not received steroids prior to trial entry for either study.

No significant differences were reported by Milman 1994 on cough (P = 0.87), dyspnoea at rest (P = 0.12), dyspnoea at exercise (P = 0.53) , sputum production (P = 0.14) and chest pain (P = 0.19).

No significant difference was reported on symptom scores by du Bois 2003.

Inhaled steroids versus placebo as an oral steroid tapering agent

One study assessed this comparison (Baughman 2002)

CXR

No data were presented on changes in radiographic scores.

Lung function

No significant change score in FVC was reported. Change in exercise capacity was reported but no details of the significance level were provided (median change: FP: 220 (feet) (-546 to +1020) versus placebo: -40 (-910 to +750).

Symptoms

There was no statistically significant on cough in both treatment groups (improved in 8/10 participants treated with FP; improved in 6/11 participants treated with placebo).

Medication usage

Baughman 2002 reported the use of oral steroids during treatment. There was no statistically significant difference between FP and placebo (FP 17 mcg/day (13-25); placebo: 17 mcg/day (9-25).

Side-effects

Comparison of toxicity was compared between FP and placebo. Edema had a lower score in participants treated with FP compared with placebo ($P < 0.005$). Depression was less common in the placebo-treated group ($P < 0.05$). However, in both instances the median score differed by one.

There were no differences between groups for treatment-associated cough, hoarseness or sore throat.

Summary of Results at Follow-up (Alberts 1995; Israel 1973; McGrath 2002; Pietinalho 1999; Roth 1975; Selroos 1979; Zaki 1987)

Seven of the eleven RCTs had follow-up data. These results could not be aggregated so are discussed individually.

Alberts 1995, followed patients up for six months after treatment with inhaled steroids for six months. Forty seven patients were randomised for the study, 32 completed the study and only 30 were left six months after follow-up. Some withdrew from the study and 11 were treated with oral steroids during the treatment period or follow-up so were excluded. Analysis of the follow-up data was confined to patients remaining in the study at the end of the six months of therapy. No statistically significant difference between the treated and control groups was found at the end of follow-up, whether in terms of CXR or lung function. Patients treated with inhaled steroids had shown an improvement in symptoms at the end of treatment but there were no further changes at follow-up. Patients who remained in the study until the end had stable disease not requiring intervention with oral steroids, so bias due to a survivor effect was present.

Israel 1973 followed up patients for 1-11 years (mean five years) after treatment with oral steroids for three months. Eighty three patients were randomised for the study and all completed it, but 38% of those given placebo and 24% given steroids required treatment with oral steroids during follow-up. In addition, eight patients needed chlorambucil because of deterioration. There was no difference between treated and control groups at follow up (mean 5.3 years) and no difference with the different radiographic stages of disease. Patients with pulmonary involvement at the onset had a worse outcome compared to those with hilar lymphadenopathy alone regardless of treatment.

Selroos 1979 followed up patients for up to 48 months after treatment with oral steroids for seven months. Thirty nine patients were randomised and thirty seven completed the treatment. Thirty two were assessed at 24 months and 25 at 48 months. Five patients were treated with steroids in the initial follow-up period and a further six were treated with steroids after 24 months because of deterioration. At the end of treatment there was a statistically significant difference between treated and control groups in FVC and DL_{CO} but this difference did not persist at follow-up. Patients whose lung function had initially improved with treatment did not maintain this improvement. There was a significant improvement in the CXR in treated patients at the end of treatment but the differences were not statistically significant at follow-up.

Zaki 1987 followed up 70% of their patients for more than three years and 35% for more than four years after treatment with oral steroids for two years. One hundred and fifty nine patients were randomised and all completed the study but many were lost to follow-up for reasons that are not made clear. There were no significant differences between treated and control groups with regard to CXR, FVC, FEV_1 or DL_{CO} at the end of treatment and there were no further changes at follow-up.

Pietinalho 1999 followed up 154 patients after treatment with either prednisolone or placebo for three months. These patients were then randomised to receive either inhaled budesonide or placebo inhaler therapy for a further fifteen months. Thirty five patients withdrew, sixteen in the treated group and nineteen in the placebo group. CXR, FVC and DL_{CO} were measured during and at the end of follow-up. They conclude that treatment is not required for patients with stage 1 disease but that an initial treatment with prednisolone followed by budesonide is more effective than placebo in patients with stage 2 disease.

McGrath 2002 assessed participants at three month follow-up post-treatment. The status of CXR was assessed between 6 and 9 months. It was reported that five/12 participants in the placebo-treated group and two/15 in the BDP-treated group had CXR's deemed 'improved'. No change was reported for five/12 placebo-treated participants and five/15 BDP-treated participants. Two/15 participants and eight/12 participants deemed to have CXRs which had deteriorated.

Roth 1975 recruited 280 patients for treatment with oral steroids for six months or 12 months and compared them to a 'no treatment' control group. They followed the patients up for 5-14 years (mean eight years) with regular radiographic and spirometric assessments. Many patients were lost to follow-up and there was no information about patients who relapsed. Treatment was discontinued in patients who experienced side-effects. There was an improvement in the CXR at the end of the first two years but no difference at subsequent follow-up. There was also no difference in the spirometric measurements at follow-up.

In summary, only in one of these follow-up studies did a difference between the treated and control groups in terms of improvement in symptoms, CXR or lung function become apparent despite an extended period of follow-up.

DISCUSSION

Treatment of pulmonary sarcoidosis with oral steroids for 6-24 months resulted in more patients having an improvement in the CXR and fewer patients having a worse CXR than in patients who received placebo. The risk ratio for improvement in CXR with oral steroid treatment was increased on average by 46% (95% CI: 1% to 109%), although the dose of oral steroid varied between the studies. However, the longer -term effects are less clear. Sub-group analysis of data from one paper (Israel 1973) showed an improvement in global scores in patients with stage 2 and 3 disease, but not with stage 1 disease. In that study, patients in the control group showed a deterioration in CXR at the end of the treatment period compared to the treated group (Erkkila 1988)

Data concerning lung function were reported in different ways so it was not possible to aggregate them in a meta-analysis. Within the individual studies, there was no significant improvement in lung function in patients treated with oral steroids although one study (Selroos 1979) showed an improvement in DLCO in the treated group. In that study, sub-group analysis showed no difference in the

change in DLCO between the different radiographic stages of the disease.

Three studies were conducted in which patients were given oral corticosteroids followed by inhaled steroids (Baughman 2002; du Bois 2003; Pietinalho 1999). The studies were of medium and long-term duration, but did not detect significant improvement in any lung function measure, symptoms and the amount of oral steroids required. The Pietinalho study looked over a 18 month period to see whether early treatment influenced the long-term prognosis and showed that although there was no significant improvement in CXR or lung function at the end of treatment , the placebo treated patients required treatment with oral steroids more frequently in the five year follow-up period. However, nearly a third of patients were lost to follow up (in both treatment and placebo groups) in the 5 year period.

There is no evidence that inhaled steroids improved CXR or lung function, although in one study (Erkkila 1988) there was a small improvement in DLCO/Va. This parameter may be the most sensitive measure of lung function in sarcoidosis, but the numbers in this study were very small. Furthermore, no actual data were given, only the number of patients who had an increase in DL_{CO}/Va greater than 15% above baseline values. In another study, there was an improvement in symptoms at the end of treatment with inhaled steroids for six months (Alberts 1995). It is now accepted that pulmonary sarcoidosis has an endobronchial component, so inhaled steroids may improve symptoms, particularly cough, by its action at this site.

It is important to note that the majority of patients in the trials of inhaled steroids had stage 1 and 2 disease, and so were perhaps less likely to show a significant improvement.

Methodological Limitations

Trials that could be included in this review used different outcome measures and presented lung function data as dichotomous or continuous data. It was not possible to combine much of the trial data for meta-analysis so there was no gain in statistical power. Often, results of symptoms or CXR changes were described as "improved", but without numerical data. Sub-group analysis was confined to differences seen with the different stages of pulmonary sarcoidosis. No other sub-group analysis was possible because of the lack of data.

Thirteen RCTs were included in this review, of which seven had data at follow up, from six months to a mean of eight years after treatment. There were data on CXR changes, lung function and symptoms. None of these studies reported a consistent beneficial effect of oral or inhaled steroids. We were unable to use the follow-up data in our review for the following reasons:

1. The follow-up studies were uncontrolled with a lack of a common end point. It was not always clear when the tests were done or at what time point the data were collected.
2. It was not clear how many patients had been lost to follow-up or the reasons for this.
3. Patients who deteriorated after the treatment period, either from the treated or the control group, were given oral steroids or other treatment, then excluded from the study. The number of patients thus excluded from the final analysis was considerable which introduces a selection bias since it excludes those patients who were worse thus introducing a survivor effect.
4. There was no blinding in the follow-up period and the assessment of patients was not done in a controlled or systematic way.

AUTHORS' CONCLUSIONS

Implications for practice

These data provide only limited guidance to physicians in the treatment of chronic pulmonary sarcoidosis. The results fit with the currently held view that patients with stage 1 disease (bilateral hilar lymphadenopathy alone) do not need treatment with oral steroids, but that those with interstitial lung disease (stages 2 and 3) may show an improvement in CXR and in global scores when treated with oral steroids. There is little evidence that treatment with oral steroids has a beneficial effect on lung function.

The available data provides little guidance for the management of this disease after 2 years. There is limited evidence that oral steroids alter disease progression and early treatment alters progression of the disease. The trials did not report side effects or complications in any standard form and the lack of reliable estimates of efficacy or details of side-effects precludes any estimate of risk-benefit ratio. Physicians treating these patients need to bear these points in mind when making management decisions after two years of therapy.

There is little evidence for the efficacy of inhaled steroids. It is well recognized that sarcoidosis is also commonly an endobronchial disease and can cause a troublesome cough. Inhaled steroids should, in theory, be beneficial for this symptom, but this is yet to be established in randomised trials. Inhaled steroids may have less systemic side effects than oral steroids and could be considered for symptom relief in those presenting with a cough.

Implications for research

Pulmonary sarcoidosis is characterised by a course that is unpredictable, with some patients showing spontaneous resolution while others progress to chronic lung disease including lung fibrosis. It is not possible currently to identify those patients who are in the latter group. Identification of this group of patients at presentation would make it possible to see if treatment with steroids in this group prevents progression of the disease to lung fibrosis.

It is known that certain ethnic groups, mainly African Americans and Afro-Caribbeans have a higher incidence of pulmonary sarcoidosis, which runs a particularly relentless course with higher morbidity and mortality. Further studies in this group of patients may identify prognostic factors. Similarly, spontaneous resolution of the disease also occurs and it would be helpful to identify markers that distinguish patients who follow such a course.

There are only a small number of randomised controlled trials in the treatment of pulmonary sarcoidosis. Much useful information could be gained from a large, multi-centre, randomised controlled trial of the effect of oral and inhaled steroids. Such a trial will need to include large numbers of patients from the African and Afro-Caribbean ethnic groups, will have to last several years and include all stages of pulmonary disease. Outcome measures should include a well-validated symptom score, measurement of lung function, CXR and CT scans of the chest, if possible. These should

be done at regular intervals. Patients who withdraw or dropout should be accounted for and followed up in the same way as those who continue. Progression to lung fibrosis must also be determined and the side effects of treatment with steroids must be well documented.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alberts 1995

Methods	DESIGN : Randomised double-blind, placebo-controlled trial. METHOD OF RANDOMISATION : Patients randomly allocated to placebo or treatment group. MEANS OF ALLOCATION CONCEALMENT : Not stated. OUTCOME ASSESSOR BLINDING : CXR for each patient was blindly reviewed by the study coordinator. WITHDRAWALS / DROPOUTS : 9 (3 in placebo group and 4 in budesonide group, 2 lost to follow up after the end of treatment). 11 were switched to prednisone due to worsening symptoms but were followed up. Only 31 completed the treatment and 30 were followed up for a further 6 months.
Participants	ELIGIBLE: Not reported. RANDOMISED : 25 placebo, 22 budesonide. COMPLETED : 22 placebo, 16 budesonide (38 total). 9 switched to steroids during treatment period. 16 placebo and 15 budesonide-treated patients completed the trial (n=31). AGE : 20 - 65 years SEX : 14 male , 11 female in placebo group, 7 male, 15 female in budesonide group. ETHNICITY : 6 non-Caucasians in placebo group, 7 non-Caucasians in budesonide group. DIAGNOSIS : Histologically confirmed pulmonary sarcoidosis. STAGES : 1 - 3 with abnormal lung function. MAJOR EXCLUSIONS : Severe symptoms requiring systemic corticosteroids, obstructive airways disease, extra pulmonary manifestations of the disease requiring treatment, pregnancy, other disease, treatment with oral steroids in the preceding 3 months. FOLLOW UP : 6 months after treatment. BASELINE : CXR, lung function tests (IVC, FEV1 and DLCO), symptoms (GCI score).
Interventions	Budesonide, 1.2 mg or placebo via a Nebuhaler for 6 months. Setting : 14 hospitals in the Netherlands.
Outcomes	Changes in CXR - improved, unchanged or worse (dichotomous) Changes in IVC, FEV1 and DLCO - continuous data. Improvement in patient symptoms (GCI score)
Notes	11 patients required oral steroids during the treatment period due to deterioration. Of these, 3 withdrew from the study. However, the end of treatment data includes these patients. In total, 17 patients were withdrawn during the study, 9 in the placebo and 8 in the budesonide group. There were 31 patients left at the end of the treatment period and 30 at 6 months after follow up. The follow up data was not therefore used in the analysis. Jadad score: 4 (R: 2; B: 1; W/D:1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	This was done by a computer in blocks for each of the centres.
Allocation concealment?	Unclear risk	Information not available

Baughman 2002

Methods	DESIGN: Randomised, double-blind, placebo-controlled study METHODS OF RANOMISATION: not reported MEANS OF ALLOCATION CONCEALMENT: Not stated. OUTCOME ASSESSOR BLINDING: Not stated. WITHDRAWAL /DROPOUTS: 1 from each group.
Participants	ELIGIBLE: Not reported. RANDOMISED: 22 (Data anlaysed for 21)

Baughman 2002 *(Continued)*

	COMPLETED: 19 AGE: FP: 43 (22-64); Placebo: 40 (33-59) SEX: 8 male ETHNICITY: African-American: 18; Caucasian: 3 DIAGNOSIS: Clinical presentation; biopsy showing noncaseating granuloma STAGE: 1-4 (1 = 8; 2 = 10; 3 = 1; 4 = 2) RECRUITMENT CRITERIA: Patients with sarcoidosis who had developed pulmonary symptoms requiring oral therapy for the first time were eligible for the study. EXCLUSION CRITERIA: Evidence of extrapulmonary disease requiring oral corticosteroid therapy (neurologic or cardiac disease); oral steroid therapy for longer than four weeks before study entry; FOLLOW-UP: 48 weeks BASELINE: FVC (L) - FP: 2.7 [1.88 to 4.93]; placebo: 2.7 [2.11 to 4.42]; FVC % predicted - FP: 80 [64 to 101]; placebo: 76 [56 to 136]; FEV1 (L) - FP: 2.16 [1.48 to 4.0]; placebo: 2.03 [1.46 to 3.68] ; FEV1 % pred - FP: 76 [69 to 103]; placebo: 79 [42 to 134]; FEV1/FVC %: FP: 81 [68 to 90]; placebo: 82 [52 to 88]; 6 min walk test: FP: 1380 [425 to 1729]; placebo: 1550 [850 to 2100]; Borg score after 6 min walk test: FP: 2.5 [0 to 5]; placebo: 3 [0.5 to 7] All participants had 'acute' disease and were being treated for the first time. Participants underwent detailed physical history looking for extra-pulmonary sarcoidosis.
Interventions	Oral steroid phase: Initial dose of prednisone (20mg @ visit 1). This was adjusted based on clinical assessment at subsequent visits and tapered or increased according to stability of disease. Once stabilised at 12 weeks participants randomised to concomitant inhaled steroids (880 mcg FP per day) or placebo.
Outcomes	1) Lung function; 2) Six minute walk test; 3) steroid consumption; 4) Withdrawals 5) Symptoms (cough) 6) Adverse effects 7) SF-36 QoL questionnaire
Notes	Jadad score: 3 (1-1-1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available

du Bois 2003

Methods	DESIGN: Randomised, double-blind, placebo-controlled study METHODS OF RANDOMISATION: not reported MEANS OF ALLOCATION CONCEALMENT : Not stated. OUTCOME ASSESSOR BLINDING : Not stated. WITHDRAWAL / DROPOUTS : 1 (prior to treatment - no data recorded)
Participants	ELIGIBLE: Not reported RANDOMISED: 43 (fluticasone: 21; placebo: 22) COMPLETED: 34 (fluticasone: 15; placebo 19) AGE : 25-65 (mean age 46.5 (SD 10.51) SEX : 17 male ETHNICITY : Caucasian: 24; Afro-carob: 14; Asian (non oriental): 5 DIAGNOSIS : CXR and positive histology. INCLUSION CRITERIA : Age between 18-65; pulmonary sarcoidosis diagnosed at least one year previously on the basis of CXR and clinical examination; positive histology; abnormal lung function (FEV1 or DLCO <75% predicted)

du Bois 2003 *(Continued)*

	STAGE : All participants had abnormal CXR (stages 2 and 3) EXCLUSIONS : Previous treatment with inhaled corticosteroids within 6 weeks of commencing treatment; changes to oral steroid regimen in previous 6 weeks; current smoker; anticipated need for heart/lung transplant in one year; inability to complete symptom card or home lung function test; co-existing medical and psychiatric conditions likely to affect or be adversely affected by participation in trial. FOLLOW UP : None after treatment. BASELINE : CXR scores: FP: 11 (1-18); placebo: 12 (7-16); airways obstruction: 34/43; Age: FP: 45 (SD 10); PLA: 48 (SD 11); oral steroids: FP: 15/21; PLA: 15/22
Interventions	Inhaled fluticasone versus placebo Duration: 6 months
Outcomes	Health status (SF 36); oral steroid usage; symptom score; Lung function;
Notes	Data could not be combined as some participants had taken oral steroids prior to study entry. Jadad score: 3 (1-1-1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available

Erkkila 1988

Methods	DESIGN: Randomised, double-blind, placebo-controlled study. METHOD OF RANDOMISATION: Not reported. MEANS OF ALLOCATION CONCEALMENT : Not stated. OUTCOME ASSESSOR BLINDING : Not stated. WITHDRAWAL / DROPOUTS : 1 in treated group due to side effects.
Participants	ELIGIBLE : Not reported. RANDOMISED : 9 for budesonide, 10 for placebo COMPLETED : 8 for budesonide, 10 for placebo. AGE : Mean 44.1, range 27 - 59. SEX : 8 male, 11 female. ETHNICITY : Not stated. DIAGNOSIS : Positive histology. INCLUSION CRITERIA : Newly detected sarcoidosis. STAGE : Stage 1 (10) and stage 2 (9) MAJOR EXCLUSIONS : Previous treatment with corticosteroids. FOLLOW UP : None after treatment. BASELINE : CXR and spirometry (DLCO/Va).
Interventions	Budesonide, 800 mcg b.d. or placebo given via identical spacers for 8 - 10 weeks.
Outcomes	CXR - changes in the size of lymph nodes and in size and number of infiltrates (dichotomous data). Spirometry - changes in DLCO/Va (dichotomous data).

Erkkila 1988 *(Continued)*

Notes	There was no information on who assessed the radiographic changes, whether this was done blindly or on inter-observer agreement. The actual data on CXR changes was minimal. An increase of > 15 % in DLCO/VA was considered a significant improvement. Jadad score: 3 (1-1-1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available

Israel 1973

Methods	DESIGN: Randomised, double-blind, placebo-controlled. METHOD OF RANDOMISATION: Consecutively numbered bottles containing steroids or placebo were randomly given to patients. MEANS OF ALLOCATION CONCEALMENT: not stated. OUTCOME ASSESSOR BLINDING: all clinical and radiological evaluations made blind. WITHDRAWALS/DROPOUTS: 83/90 completed the study. 38%receiving placebo and 24% receiving prednisone required prednisone subsequently for relapse or pregression of disease.
Participants	ELIGIBLE: 90 recruited. RANDOMISED: 41 for prednisone (20 stage 1 and 21 stages 2 and 3) and 42 for placebo (17 stage 1 and 25 stages 2 and 3). AGE: all ages, mean between 21 and 40. DIAGNOSIS: active sarcoidosis by clinical, laboratory and histologic methods. STAGE: 37 stage 1 and 46 stages 2 and 3. SEX: 23 male and 60 female. ETHNICITY: 75 african, 7 caucasian and 1 Puerto-Rican RECRUITMENT: over a 5 year period. EXCLUSIONS: patients with uveitis, hypercalcaemia, acute respiratory distress, patients previously treated and those with irreversible fibrosis. BASELINE: clinical, radiological and spirographic measurements.
Interventions	Prednisone, 15 mg o.d or placebo for a 3 month period.
Outcomes	Clinical, radiological and spirographic assessment, grouped together (global). Assessments made at the end of treatment (3-month trial) and after a mean interval of 5.3 years (1 - 11 years). 3 deaths in the follow-up period.
Notes	No data available on radiological or spirographic measurements alone. 90 patients recruited but only 83 completed trial. No information on why patients dropped out. Subsequent corticosteroid therapy appeared to be indicated in 20 % of those originally receiving prednisone and in 30 % of those originally in the placebo group. 8 patients received chlorambucil therapy due to severe disease not responding to prednisone. The patients who were treated with further steroids after the treatment period were included in the follow-up analysis. Therefore, the follow-up data was not used . Jadad score: 4 (2-1-1)

Risk of bias

Israel 1973 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Low risk	Consecutively numbered bottles containing steroids or placebo were randomly given to patients

James 1967

Methods	DESIGN: Randomised double-blind controlled trial. RANDOMISATION: Not reported. MEANS OF ALLOCATION CONCEALMENT: the tablets were represented in the allocation by three code symbols and patients given identical tablets. BLINDING: treatment unknown to clinician, dispenser or the patient. WITHDRAWALS/DROPOUTS: 9 patients (3 each on prednisolone, oxyphenbutazone and placebo) did not complete the course because 7 defaulted, 1 became pregnant and 1 was given steroids. OUTCOME ASSESSOR BLINDING : CXR changes were serially assessed at the beginning and at the end of 6 months by a clinician and a radiologist unaware of the treatment schedule.
Participants	ELIGIBLE: 84 RANDOMISED: 30 prednisolone, 27 oxyphenbutazone and 27 placebo. COMPLETED: 27 prednisolone, 24 oxyphenbutazone and 24 placebo. AGE: range 0 - 60 (as described by authors in Table 2). SEX: 42 male, 33 female. DIAGNOSIS : Histologically confirmed. RECRUITMENT CRITERIA : Evidence of multisystem disease and CXR changes in patients attending a sarcoidosis clinic. EXCLUSION CRITERIA: any treatment with trial drugs or other active treatment in the preceding 6 months. Also those with contraindications to treatment. Comparable distribution in age, sex and race. BASELINE : CXR (39 with stage 1, 25 with stage 2 and 11 with stage 3 disease)
Interventions	Prednisolone 5mg, oxyphenbutazone 100 mg and placebo (containing lactose) given qds for 6 months.
Outcomes	CXR changes (dichotomous data).
Notes	The oxyphenbutazone group is not included in this review. 10 patients were reallocated into the trial after a lapse of > 6 months from their previous course of treatment (which was unknown). There was no data on symptoms and there was no follow-up data. Jadad score: 4 (1-2-1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Low risk	Tablets were represented in the allocation by three code symbols and patients given identical tablets.

Ludwig 2005

Methods	DESIGN : Randomised double-blind, placebo-controlled trial. METHOD OF RANDOMISATION : Patients randomly allocated to placebo or treatment group. MEANS OF ALLOCATION CONCEALMENT : Not stated. BLINDING: Identical inhaler device used OUTCOME ASSESSOR BLINDING : CXR for each patient was blindly reviewed by a radiologist. WITHDRAWALS / DROPOUTS : None occurred.
Participants	ELIGIBLE: Not stated RANDOMISED: 15 (treatment 6: control: 9) COMPLETED: 15 AGE (mean): 35 years SEX: 9M. RECRUITMENT CRITERIA: Pulmonary sarcoidosis at radiological stages I-III. EXCLUSION CRITERIA: Use of inhaled steroids 4 weeks prior to study entry; systemic corticosteroid rx in previous three months. BASELINE CHARACTERISTICS: CXR staging: Placebo group - Normal/i: 3; ii: 5; iii: 1; BDP group: Normal/i: 0; ii: 0; iii: 6. Disease duration: 4 (1-18) months. FEV1: 97% predicted; TLco: 83% predicted
Interventions	800mcg (2x400mcg) HFA-BDP per day day versus placebo via Autohaler Duration: 12 weeks
Outcomes	1) Lung function (FEV1; TLco) 2) Exercise capacity 3) CXR
Notes	Jadad score: 5 (2-2-1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer-generated randomisation schedule (RPAS 3, version 1.52 of EQUILA from Episys Ltd (correspondence from trialist)
Allocation concealment?	Unclear risk	Information not available

McGrath 2002

Methods	DESIGN: Randomised double-blind parallel group trial. METHOD OF RANDOMISATION: Not reported. MEANS OF ALLOCATION CONCEALMENT: Not reported. BLINDING: Study reported as 'Double-blind' WITHDRAWALS: Two participants withdrew from the study before recording any data. After randomisation, one and two participants withdrew from the treatment and control groups respectively. Data missing for a further participant randomised to placebo and not acccounted for.
Participants	ELIGIBLE: Not stated RANDOMISED: 31(treatment: 16; control: 15) COMPLETED: 27 AGE: 47.7 (SD 10.27) SEX: M: 11 male (uneven distribution at baseline between active and placebo treatments: BDP group: 9/16 versus Placebo group: 2/15). RECRUITMENT CRITERIA: Age 18-65; sarcoidosis with abnormal lung function (FEV1 or DLCO<15% presenatation value) and/or CXR evidence of parenchymal disease (Stage II, III or IV) EXCLUSION CRITERIA: Use of inhaled steroids 6 weeks prior to study entry; IV or depot corticosteroid rx in previous three months; change in dose of oral steroids in six weeks before entry; rapidly progressive

McGrath 2002 *(Continued)*

	disease likely to require 'escape therapy' during the 6 month period; known hypersensivity to inhlaed steroids; inability to use autohaler device correctly BASELINE CHARACTERISTICS: CXR staging: Placebo group - Normal/i: 3; ii: 3; iii: 3; iv: 3. BDP group: Normal/i: 2; ii: 3; iii: 4; iv: 6. Disease duration: 9.6 +/-6.95 years. Smoking status: Never 20; ex-smoker: 10; current: 1.
Interventions	1600mcg (2x800 mcg) BDP per day versus placebo Duration: Not clear
Outcomes	1) Lung function (FEV1 and DLCO) 2) Radiology 3) Biochemistry 4) Reactivation of sarcoidosis 5) Adverse events
Notes	Baseline imbalance between active and placebo treated participants on CXR Jadad score: 3 (1-1-1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available

Milman 1994

Methods	DESIGN Randomised double-blind placebo controlled parallel group trial. METHOD OF RANDOMISATION: Not reported. MEANS OF ALLOCATION CONCEALMENT: Not reported. BLINDING: Study reported as 'Double-blind' WITHDRAWALS: Four participants withdrew after 6 months of treatment. Data analysed on an intention-to-treat principle.
Participants	ELIGIBLE: Not stated RANDOMISED: 21 (treatment: 9, placebo: 12) COMPLETED: 17 (ITT data analysed) AGE: median: 33 years (21-65) SEX: 17M RECRUITMENT CRITERIA: Age 18-60; able to use inhaler device; radiological stage 1-3 pulmonary sarcoidosis verified by biopsy. EXCLUSION CRITERIA: Pregnancy/planned pregnancy; previous or present infection with mycobacteria; present pulmonary infection. BASELINE CHARACTERISTICS: Duration of disease: 13 months (range: 2-192); median duration of biopsy verified disease: 5 months (range: 1-188); four participants had extrapulmonary symptoms; eight participants were on oral prednisolone (2.5-30 mg /day)
Interventions	Inhaled budesonide 1.2 mg/day versus placebo Data stratified for three treatment regimens - group 1 and 2(untreated participants with sarcoidosis) and group 3 participant with sarcoidosis treated with systemic steroids Duration: 12 months

Milman 1994 *(Continued)*

	All participants followed for 18 months
Outcomes	Withdrawals; CXR; FEV1; FVC; FEV1/FVC %; RV; TLC; gallium scintigraphy (ratio); symptoms
Notes	Jadad 3 score (1-1-1). Eight participants on oral steroids at baseline. Five participants had to start on oral steroid therapy during the treatment period of the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available

Pietinalho 1999

Methods	DESIGN: Randomised multi-centre, double-blind placebo controlled trial. METHODS OF RANDOMISATION: Not reported. MEANS OF ALLOCATION CONCEALMENT: Not reported. OUTCOME ASSESSOR BLINDING: Not reported. WITHDRAWALS/DROPOUTS: 19 in placebo group and 16 in steroid group. Data analysed as ITT population.
Participants	ELIGIBLE: 190 RANDOMISED: 189 (92 to budesonide; 97 to placebo) COMPLETED: 18 month study: 154; 5 year follow-up: 132. AGE: 40.4 (SD: 10.5) SEX: 105M DIAGNOSIS: Positive tissue biopsy finding (92 participants); positive needle aspiration (23 participants); positive Kveim test (3 participants); elevated SACE values (67 participants) RECRUITMENT CRITERIA: >/= 18 years of age; newly diagnosed (<3 months) radiographic stage I or II pulmonary sarcoidosis with typical clinical picture of sarcoidosis; positive tissue biopsy/cytological finding, increased SACE activity, positive Kveim test desirable but not obligatory. EXCLUSION CRITERIA: Lung disease other than pulmonary sarcoidosis (I-III); erythema nosodum; pulmonary fibrosis; extrapulmonary sarcoidosis requiring immediate treatment with oral steroids; patients receiving steroid treatment for other reasons; pregnant and lactating women; patients with other specified, poorly controlled disease. BASELINE CHARACTERISTICS: Ex-smokers: 46; Stage I disease: 94 (PRED+BUD: 48; placebo: 46); Stage II disease: 84 (PRED+BUD: 38; placebo: 46); Stage III disease: 11 (PRED+BUD: 6; placebo: 5). Duration of disease: 29 (SD: 27.62 days); Symptom free: 24 (PRED+BUD: 11; placebo: 13).
Interventions	Oral PRED (20mg/d for eight weeks; 15mg/d for two weeks and 10mg/d for two weeks) versus placebo (duration: 12 weeks) followed by 1600mcg BUD versus placebo (duration: 15 months). Participants randomised to oral PRED received BUD and participants randomised to placebo tablets received placebo inhaler.
Outcomes	1) CXR 2) Lung function (FEV1; FVC; DLCO) 3) SACE (U/mL) 4) Laboratory test values (serum ß2-microglobulin; serum calcium; serum cortisol)

Pietinalho 1999 *(Continued)*

Notes	Jadad: 3 (1-1-1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised in blocks of four.
Allocation concealment?	Unclear risk	Information not available

Roth 1975

Methods	DESIGN: Randomised controlled study (no placebo treatment) METHOD OF RANDOMISATION: Not reported. MEANS OF ALLOCATION CONCEALMENT: Not stated. OUTCOME ASSESSOR BLINDING: Yes. WITHDRAWAL/DROPOUTS: 19 (protocol violations); 12 (side-effects). Not explicit which groups these participants were allocated to. No ITT analysis
Participants	ELIGIBLE: Not reported. RANDOMISED: 280. COMPLETED: 172 (available at 5 year follow-up to 14 year follow-up). AGE: 20-29: N = 18; 30-39: N = 70; 40-49: N = 55; 50-59: N = 16; 60-69: N = 12 SEX: 87M; 85W ETHNICITY: Not reported DIAGNOSIS: Biopsy; pulmonary sarcoidosis classified by CXR as stage 1, 2 or 3 INCLUSION CRITERIA: Diagnosis of sarcoidosis STAGE: 1-3 (1: N = 67; 2: N = 75; 3: N = 30) MAJOR EXCLUSIONS: Extra-pulmonary sarcoidosis. FOLLOW UP: 3-14 years (See Notes) BASELINE: Complete lung function data and symptoms at baseline are not available
Interventions	Three treatment groups: Two 'active' intervention groups received (A1 and A2): 40 mg daily prednisolone for 4 weeks followed by reduction in dose of 5mg per day until a maintenance dose of 10mg per day was achieved. Group A1 received treatment for 12 months and Group A2 received treatment for 6 months. Group B received no treatment. Data are reported for 172 participants at follow up. No data are reported at end of treatment - all available data are reported for follow-up periods >/= 3 years.
Outcomes	Resolution of sarcoidosis; Relapse; Lung function (FEV1; DLCO; PaO2; FVC; DM);
Notes	Randomised study conducted over 19 years. Participants continually recruited. Jadad score: 1 (1-0-0*) *Withdrawals inadequately reported for all randomised participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; no other information available
Allocation concealment?	Unclear risk	Information not available

Selroos 1979

Methods	DESIGN :Randomised, no blinding, no placebo treatment administered. RANDOMISATION : A sealed code envelope was drawn. MEANS OF ALLOCATION CONCEALMENT : Not stated. BLINDING : None OUTCOME ASSESSOR BLINDING : Not stated. WITHDRAWALS/DROPOUTS : 2 withdrawn as they did not follow the planned regimen.
Participants	ELIGIBLE: 39 RANDOMISED: 39 COMPLETED : 37 at end of treatment, 32 at 24 months and 25 at 48 months. AGE : not stated. SEX : 18 male, 19 female. ETHNICITY : Not stated (probably FIinnish). DIAGNOSIS : Positive histology or positive Kveim. STAGE : stage 2 disease of < 5 years duration. RECRUITMENT CRITERIA : EXCLUSION CRITERIA : Treatment previously with corticosteroids, extrapulmonary lesions. FOLLOW UP : At 24 months and 48 months after treatment.
Interventions	Methylprednisolone, in varying doses (from 32 mg down to 4 mg per day) given either every day or on alternate days for 7 months versus a no treatment group.
Outcomes	CXR changes (dichotomous data). Spirometry (FVC and DLCO - continuous data).
Notes	Patients in the no treatment group who deteriorated symptomatically were treated with methylprednisolone. These patients and those in the treatment group who were treated for longer than 7 months were excluded from further evaluations.Patients were followed up for 48 months with data at 24 and 48 months. 32 patients were still in the study at 24 months and 25 were in the study at 48 months. The follow-up data was not used. Jadad score: 3 (2-0-1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; no other information available
Allocation concealment?	Low risk	A sealed code envelope was drawn.

Zaki 1987

Methods	DESIGN: Randomised, double-blind, placebo-controlled trial. METHOD OF RANDOMISATION : A randomised block design was used. MEANS OF ALLOCATION CONCEALMENT : Not stated. OUTCOME ASSESSOR BLINDING : A double-blind technique used. WITHDRAWAL / DROPOUTS: 24 / 183 excluded because of lack of cooperation, relocation, other medical problems or death.
Participants	ELIGIBLE: 183 RANDOMISED: 94 prednisone and 65 placebo (159). COMPLETED: 94 prednisone and 65 placebo (159). AGE: Range < 25 to > 45 (majority < 35).

Zaki 1987 *(Continued)*

	SEX: 75% female, 25% male. DIAGNOSIS: Histological and clinical. STAGES: Stage 1 (38 prednisone, 26 placebo), stage 2 (34 prednisone, 25 placebo), stage 3 (13 prednisone, 6 placebo), non-pulmonary (9 prednisone, 8 placebo). DURATION OF DISEASE: < 6 months (50 prednisone, 36 placebo), 6 - 12 months (25 prednisone, 17 placebo), > 12 months (19 prednisone, 12 placebo). RECRUITMENT: Hospital clinic. EXCLUSION: Evidence of other granulomatous disease, other therapy. BASELINE: Clinical assessment, CXR and pulmonary function (FVC, FEV1, DLCO and PO2). FOLLOW UP: >70% for > 3 years and 35% for 4 years.
Interventions	Prednisone, 40 mg o.d. for 3 months, followed by 20 mg o.d. for 2 years as treatment. Control group received similar number of inert tablets.
Outcomes	CXR (dichotomous data). Lung function (FVC, FEV1 and DLCO) - dichotomous data).
Notes	Patients receiving other medication were excluded from the final analysis. It is stated that "In most instances the originally prescribed course of therapy was followed". It was not clear why patients were lost to follow up, whether due to deterioration or to treatment. Changes in lung function of + 10 % were felt to be significant. Jadad score: 3 (1-1-1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	'Within each block, patients were matched in pairs according to age, sex, ethnicity and duration of disease. One member of each pair was then assigned at random to the study group and the other to the control group.'
Allocation concealment?	Unclear risk	Information not available

CXR: chest x-ray; FEV1: forced expiratory volume in one second; DLCO: diffusing capacity; FVC: Forced vital capacity; Rx: treatment; BDP: beclomethasone; BUD: budesonide; PRED: prednisolone; FP: fluticasone; SACE: serum lysozyme angiotensin-converting enzyme; QoL: Quality of life; ITT: intention-to-treat; RV: residual volume: TLC: total lung capacity; PaO2: oxygen arterial pressure; DM: membrane diffusing capacity

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Baughman 2002a	Review article
Doboch 2000	Not randomised.
Ebell 2005	Review article.
Gibson 1996	Not a randomised, double-blind placebo controlled trial.
Gilleran 2002	Review article
Harkleroad 1982	A prospective study.
Hoyles 2005	Study of multiple treatment regimens in pulmonary fibrosis

Study	Reason for exclusion
Hunninghake 1994	A prospective study.
Johns 1986	Not a randomised controlled trial.
Pietinalho 1991	Not a placebo-controlled trial.
Selroos 1986	Not a randomised double-blind placebo-controlled trial.
Selroos 1994a	Not a randomised double-blind placebo-controlled trial.
Spratling 1985	Daily versus alternate day treatment with prednisone. No control group.
Zych 1987	Not a placebo-controlled trial.
Zych 1992	Not a placebo-controlled trial (comparison of inhaled budesonide vs oral prednisone).
Zych 1993	Not a placebo-controlled trial.

DATA AND ANALYSES

Comparison 1. Oral steroids versus placebo

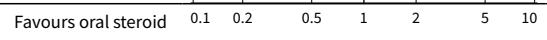
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global (CXR, clinical,spirographic) - improved after 6 months of treatment.	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.42, 0.90]
1.1 Stage 1	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.38, 1.27]
1.2 Stages 2 and 3	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.35, 0.92]
2 Global (CXR, clinical,spirographic) - unchanged after 6 months treatment	1	83	Risk Ratio (M-H, Fixed, 95% CI)	2.47 [1.46, 4.19]
2.1 Stage 1	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [1.06, 3.57]
2.2 Stages 2 and 3	1	46	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [1.35, 9.44]
3 Global (CXR, clinical,spirographic) - worse after 6 months treatment	1	83	Risk Ratio (M-H, Fixed, 95% CI)	4.04 [0.73, 22.48]
3.1 Stage 1	1	37	Risk Ratio (M-H, Fixed, 95% CI)	4.25 [0.55, 32.93]
3.2 Stages 2 and 3	1	46	Risk Ratio (M-H, Fixed, 95% CI)	3.55 [0.15, 82.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 CXR (improved)	3	370	Risk Ratio (M-H, Random, 95% CI)	1.46 [1.01, 2.09]
4.1 All stages	3	370	Risk Ratio (M-H, Random, 95% CI)	1.46 [1.01, 2.09]
5 CXR (unchanged)	3	370	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.43, 0.92]
5.1 All stages	3	370	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.43, 0.92]
6 CXR (worse)	3	370	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.18, 0.87]
6.1 All stages	3	370	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.18, 0.87]
7 FEV1 (dichotomous data) - improved	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.79, 1.11]
7.1 Stage 1	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.70, 1.19]
7.2 Stage 2	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.79, 1.18]
8 FEV1 (dichotomous data) - unchanged	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.78, 1.20]
8.1 Stage 1	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.86, 1.32]
8.2 Stage 2	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.57, 1.29]
9 FEV1 (dichotomous data) - worse	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 Stage 1	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Stage 2	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 FVC (dichotomous data) - improved	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.63, 1.13]
10.1 Stage 1	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.59, 1.31]
10.2 Stage 2	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.53, 1.24]
11 FVC (dichotomous data) - unchanged	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.66, 1.90]
11.1 Stage 1	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.64, 3.07]
11.2 Stage 2	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.45, 1.87]
12 FVC (dichotomous data) - worse	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.29, 1.09]
12.1 Stage 1	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.20, 1.19]
12.2 Stage 2	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.25, 1.78]

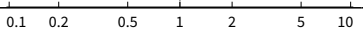
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 FVC (% predicted)	1	119	Mean Difference (IV, Fixed, 95% CI)	3.58 [-1.20, 8.37]
13.1 Stage 1	1	61	Mean Difference (IV, Fixed, 95% CI)	0.10 [-7.37, 7.57]
13.2 Stage 2	1	58	Mean Difference (IV, Fixed, 95% CI)	6.00 [-0.23, 12.23]
14 DLCO(dichotomous data) - improved	1	87	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.62, 1.23]
14.1 Stage 1	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.60, 1.33]
14.2 Stage 2	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.47, 1.55]
15 DLCO(dichotomous data) - unchanged	1	87	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.58, 1.47]
15.1 Stage 1	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.9 [0.52, 1.57]
15.2 Stage 2	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.42, 2.18]
16 DLCO(dichotomous data) - worse	1	87	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.27, 2.04]
16.1 Stage 1	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.22, 3.39]
16.2 Stage 2	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.15, 2.79]
17 DLCO (% predicted)	1	119	Mean Difference (IV, Fixed, 95% CI)	2.79 [-3.71, 9.30]
17.1 Stage 1	1	61	Mean Difference (IV, Fixed, 95% CI)	1.20 [-7.72, 10.12]
17.2 Stage 2	1	58	Mean Difference (IV, Fixed, 95% CI)	4.60 [-4.90, 14.10]

Analysis 1.1. Comparison 1 Oral steroids versus placebo, Outcome 1 Global (CXR, clinical,spirographic) - improved after 6 months of treatment..

Study or subgroup	Oral corticosteroid n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Stage 1					
Israel 1973	9/20	11/17		38.28%	0.7[0.38,1.27]
Subtotal (95% CI)	**20**	**17**		**38.28%**	**0.7[0.38,1.27]**
Total events: 9 (Oral corticosteroid), 11 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.19(P=0.23)					
1.1.2 Stages 2 and 3					
Israel 1973	10/21	21/25		61.72%	0.57[0.35,0.92]
Subtotal (95% CI)	**21**	**25**		**61.72%**	**0.57[0.35,0.92]**
Total events: 10 (Oral corticosteroid), 21 (Placebo)					



Study or subgroup	Oral corti-costeroid n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=2.32(P=0.02)					
Total (95% CI)	**41**	**42**		**100%**	**0.62[0.42,0.9]**
Total events: 19 (Oral corticosteroid), 32 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.27, df=1(P=0.6); I^2=0%					
Test for overall effect: Z=2.54(P=0.01)					
Test for subgroup differences: Not applicable					

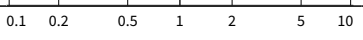


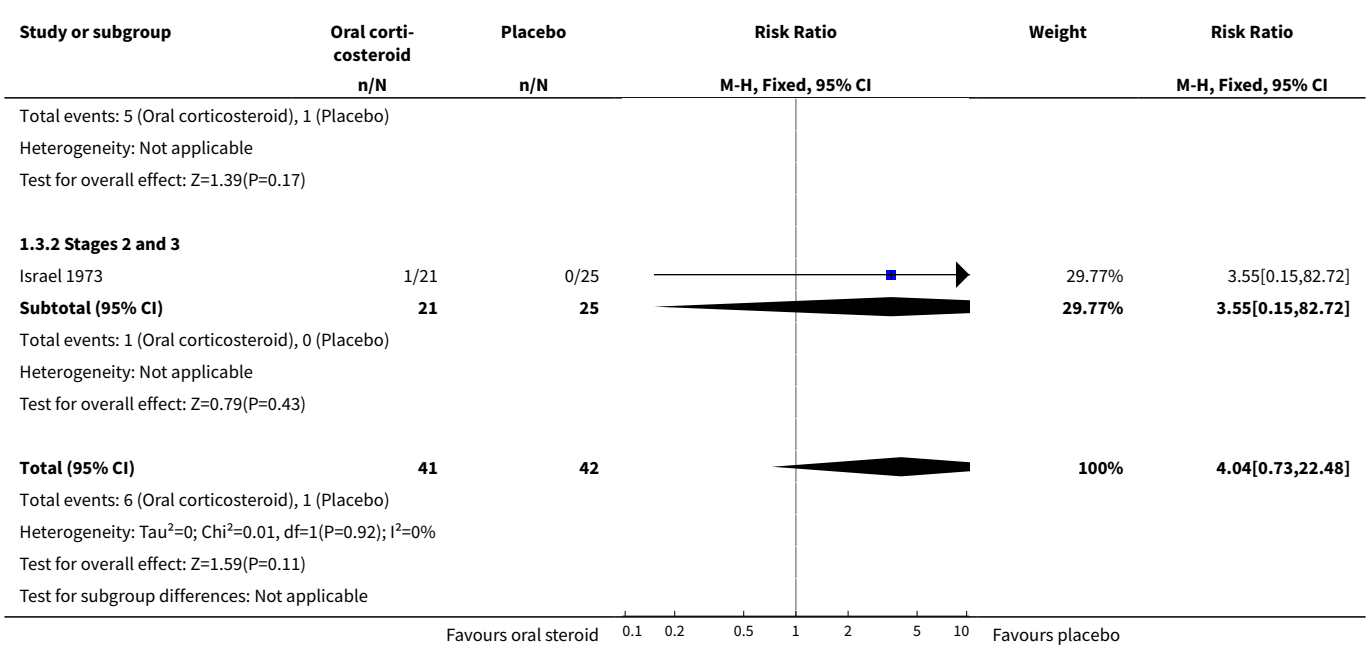
Analysis 1.2. Comparison 1 Oral steroids versus placebo, Outcome 2 Global (CXR, clinical,spirographic) - unchanged after 6 months treatment.

Study or subgroup	Oral corti-costeroid n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Stage 1					
Israel 1973	16/20	7/17		67.45%	1.94[1.06,3.57]
Subtotal (95% CI)	**20**	**17**		**67.45%**	**1.94[1.06,3.57]**
Total events: 16 (Oral corticosteroid), 7 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.14(P=0.03)					
1.2.2 Stages 2 and 3					
Israel 1973	12/21	4/25		32.55%	3.57[1.35,9.44]
Subtotal (95% CI)	**21**	**25**		**32.55%**	**3.57[1.35,9.44]**
Total events: 12 (Oral corticosteroid), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.57(P=0.01)					
Total (95% CI)	**41**	**42**		**100%**	**2.47[1.46,4.19]**
Total events: 28 (Oral corticosteroid), 11 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.15, df=1(P=0.28); I^2=13.25%					
Test for overall effect: Z=3.37(P=0)					
Test for subgroup differences: Not applicable					

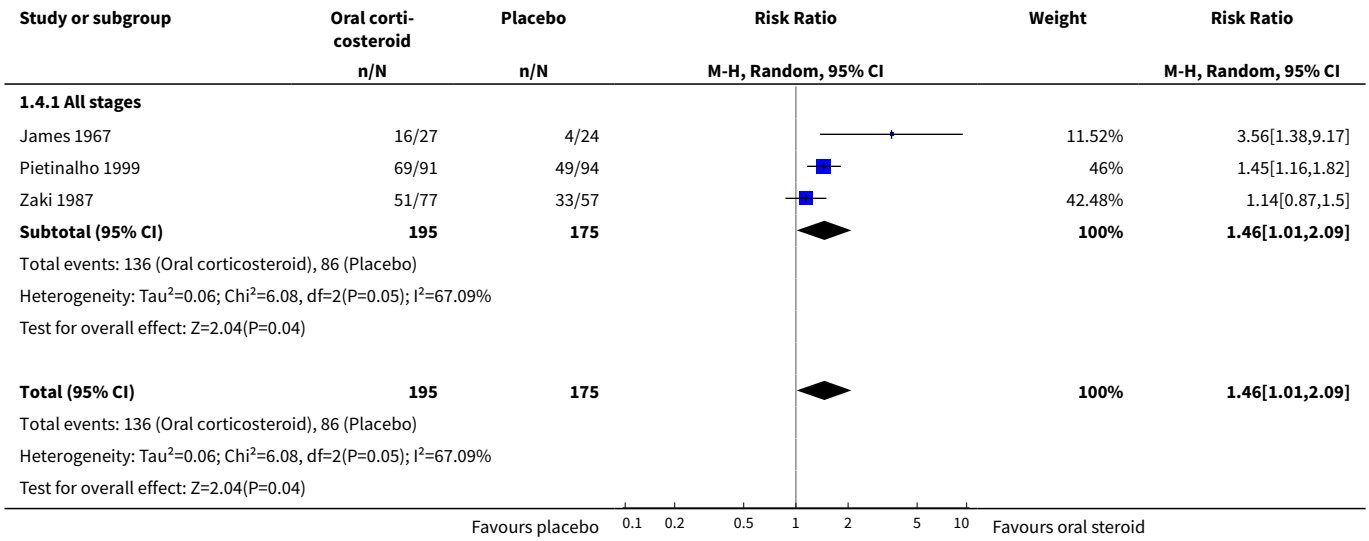
Analysis 1.3. Comparison 1 Oral steroids versus placebo, Outcome 3 Global (CXR, clinical,spirographic) - worse after 6 months treatment.

Study or subgroup	Oral corti-costeroid n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Stage 1					
Israel 1973	5/20	1/17		70.23%	4.25[0.55,32.93]
Subtotal (95% CI)	**20**	**17**		**70.23%**	**4.25[0.55,32.93]**

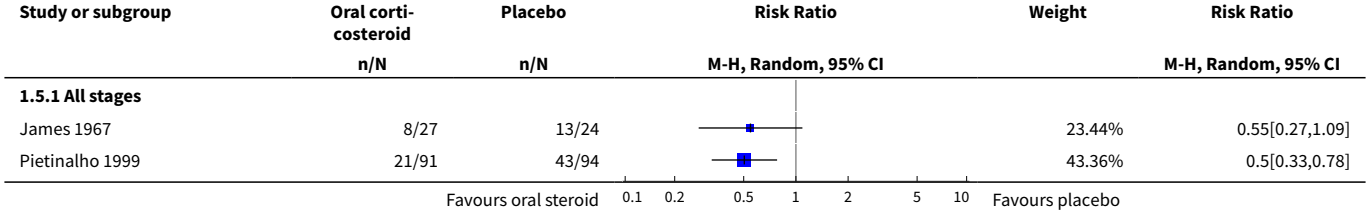


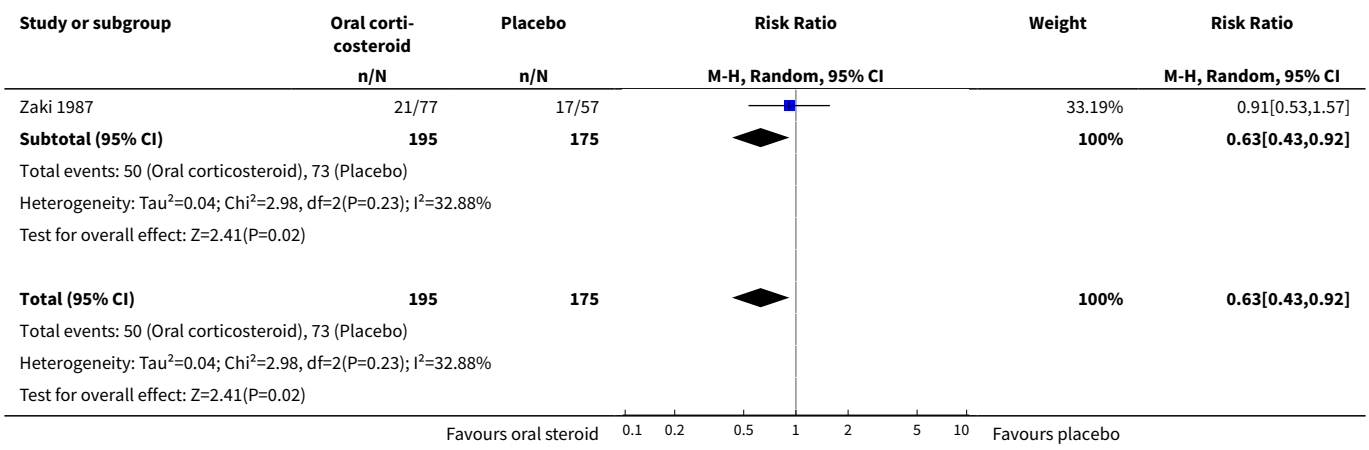


Analysis 1.4. Comparison 1 Oral steroids versus placebo, Outcome 4 CXR (improved).

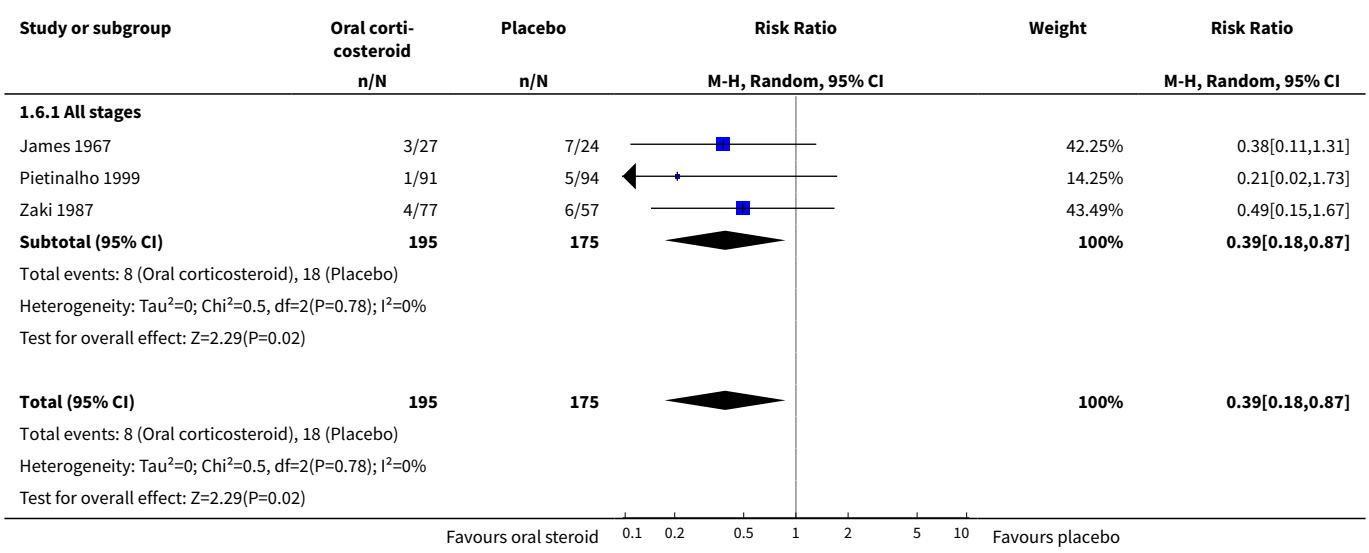


Analysis 1.5. Comparison 1 Oral steroids versus placebo, Outcome 5 CXR (unchanged).

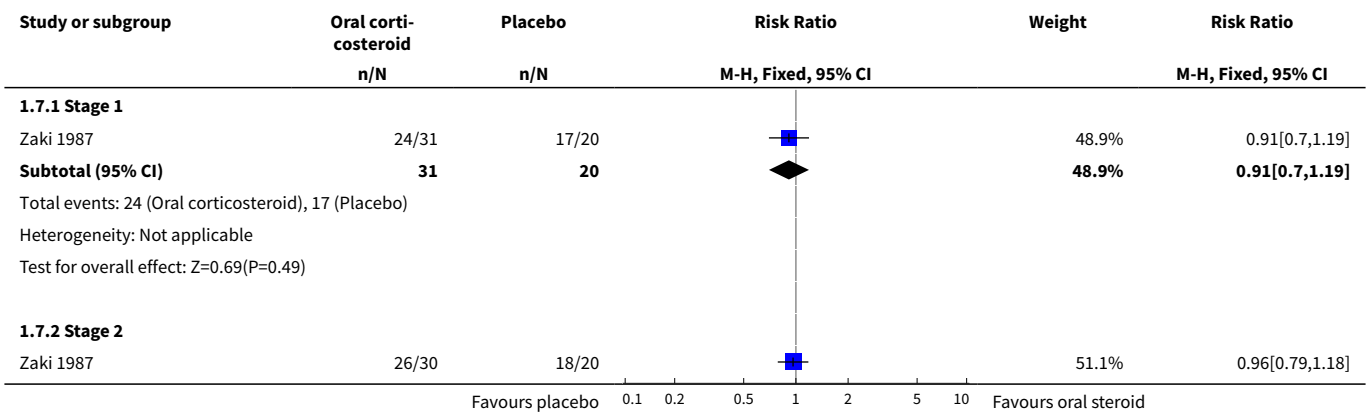


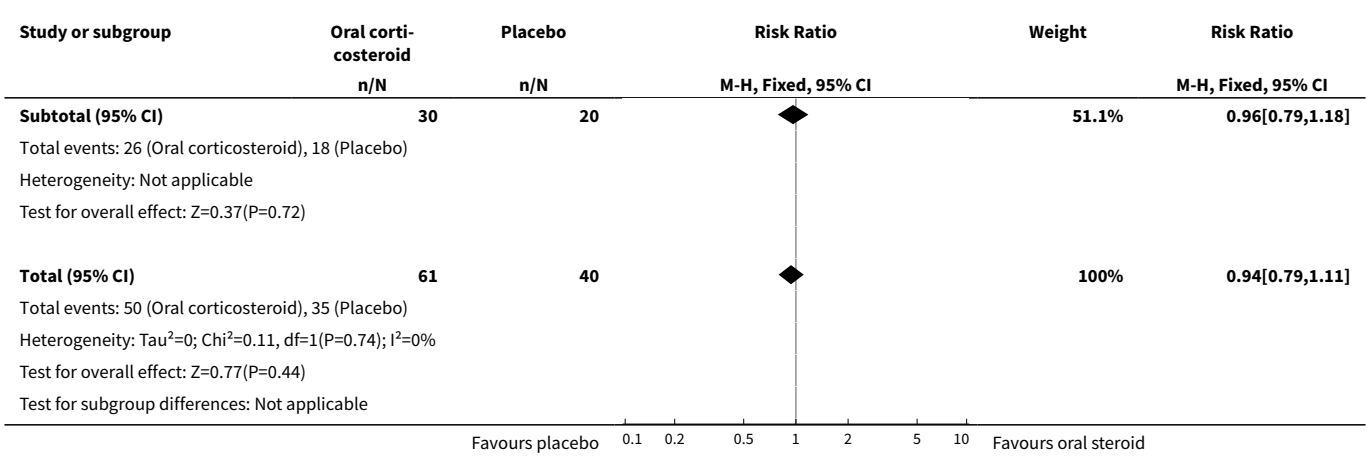


Analysis 1.6. Comparison 1 Oral steroids versus placebo, Outcome 6 CXR (worse).

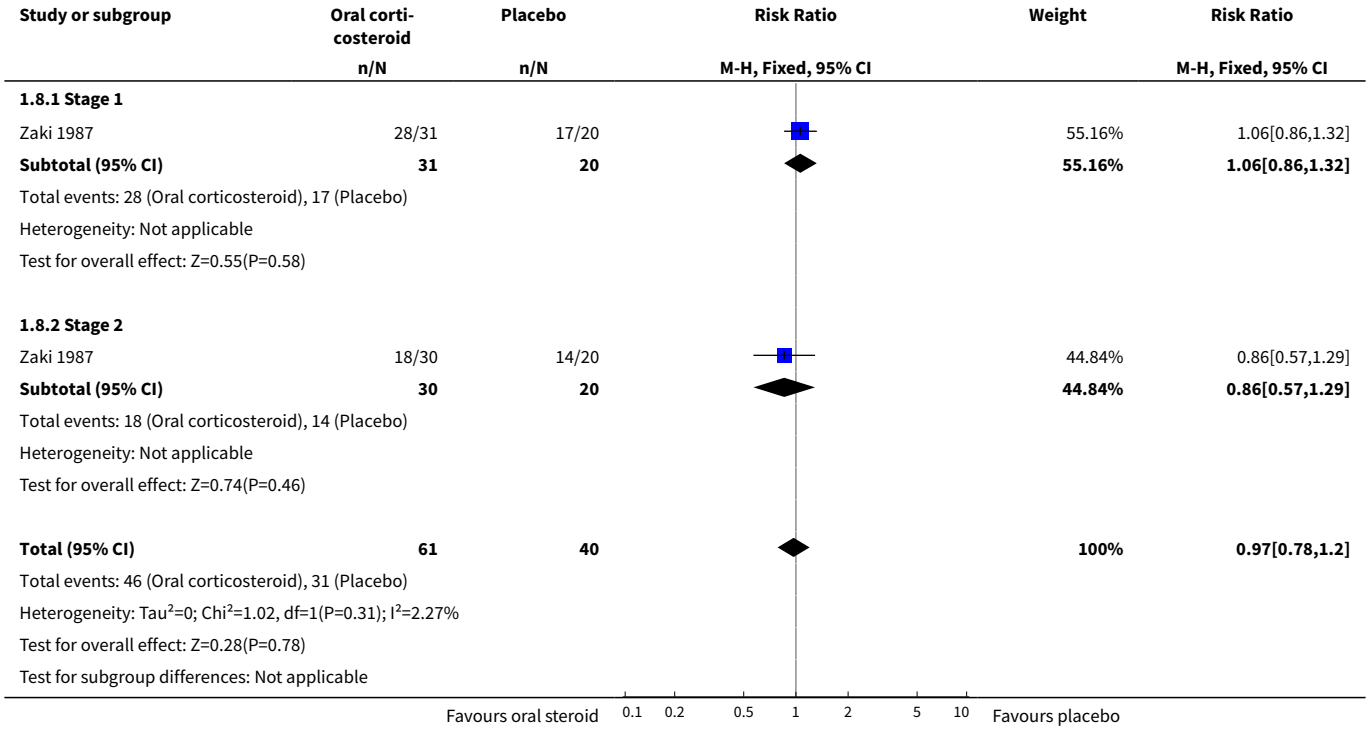


Analysis 1.7. Comparison 1 Oral steroids versus placebo, Outcome 7 FEV1 (dichotomous data) - improved.

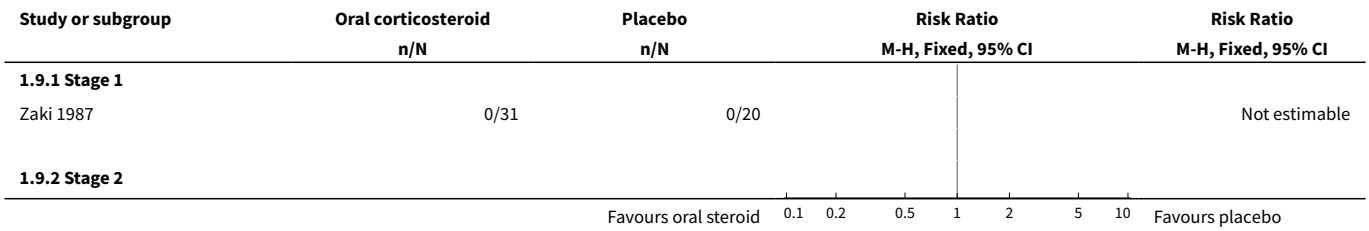


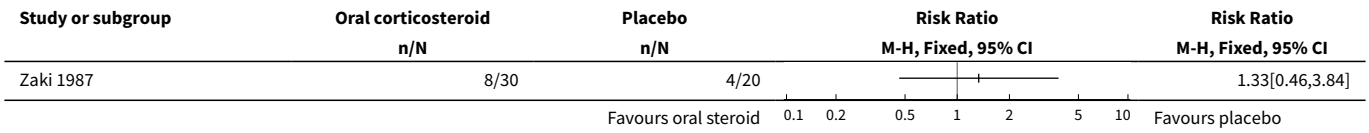


Analysis 1.8. Comparison 1 Oral steroids versus placebo, Outcome 8 FEV1 (dichotomous data) - unchanged.

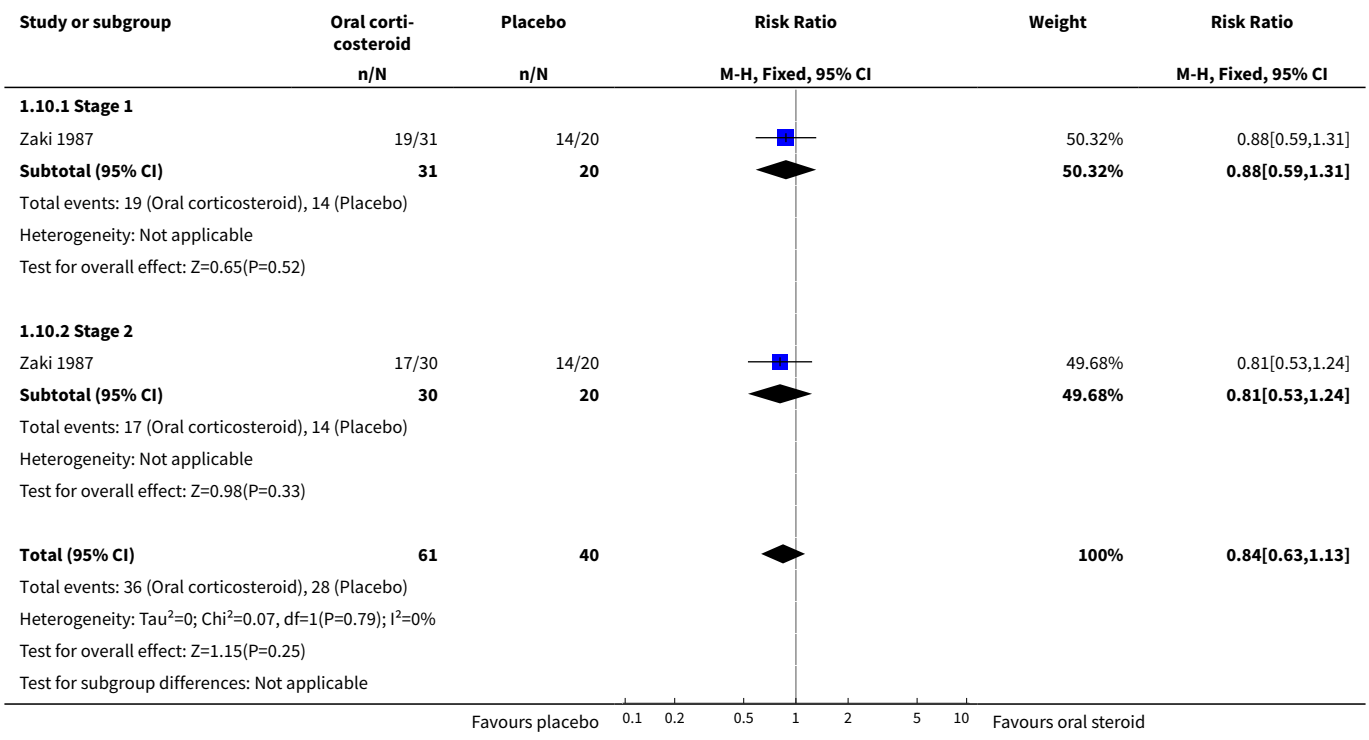


Analysis 1.9. Comparison 1 Oral steroids versus placebo, Outcome 9 FEV1 (dichotomous data) - worse.

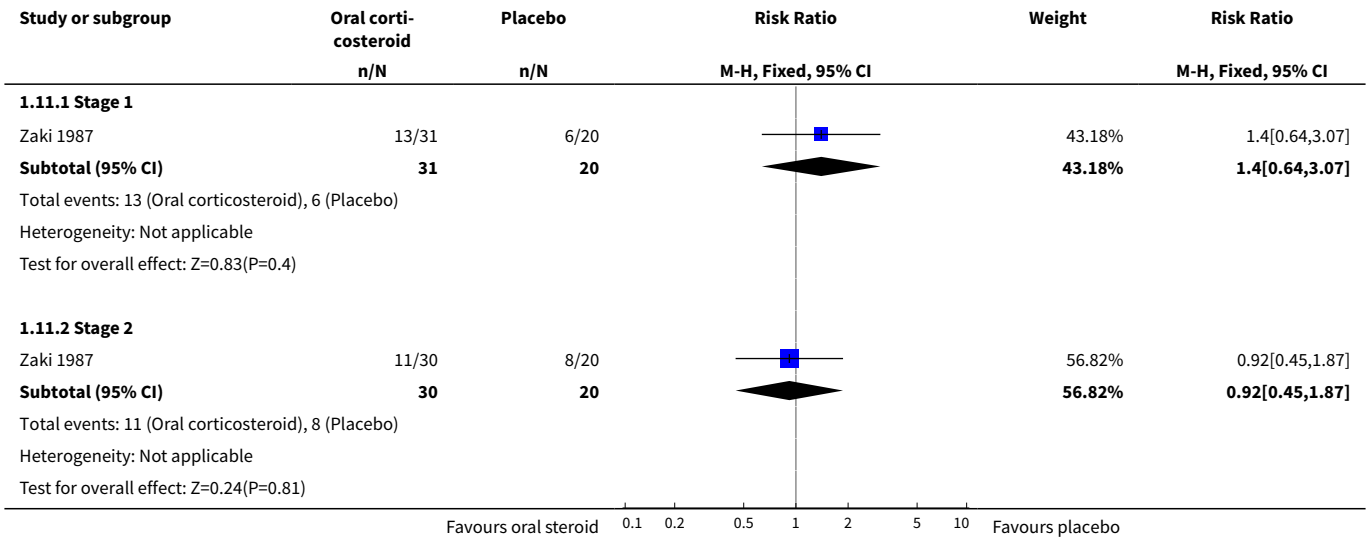


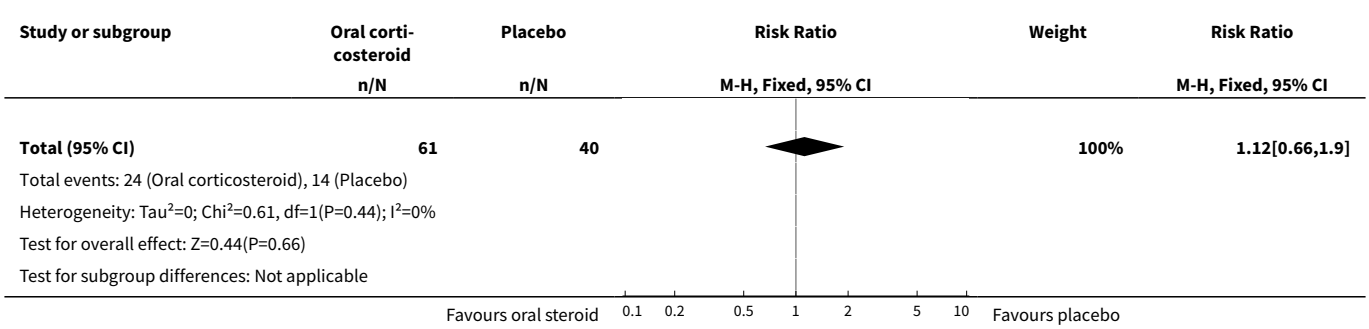


Analysis 1.10. Comparison 1 Oral steroids versus placebo, Outcome 10 FVC (dichotomous data) - improved.

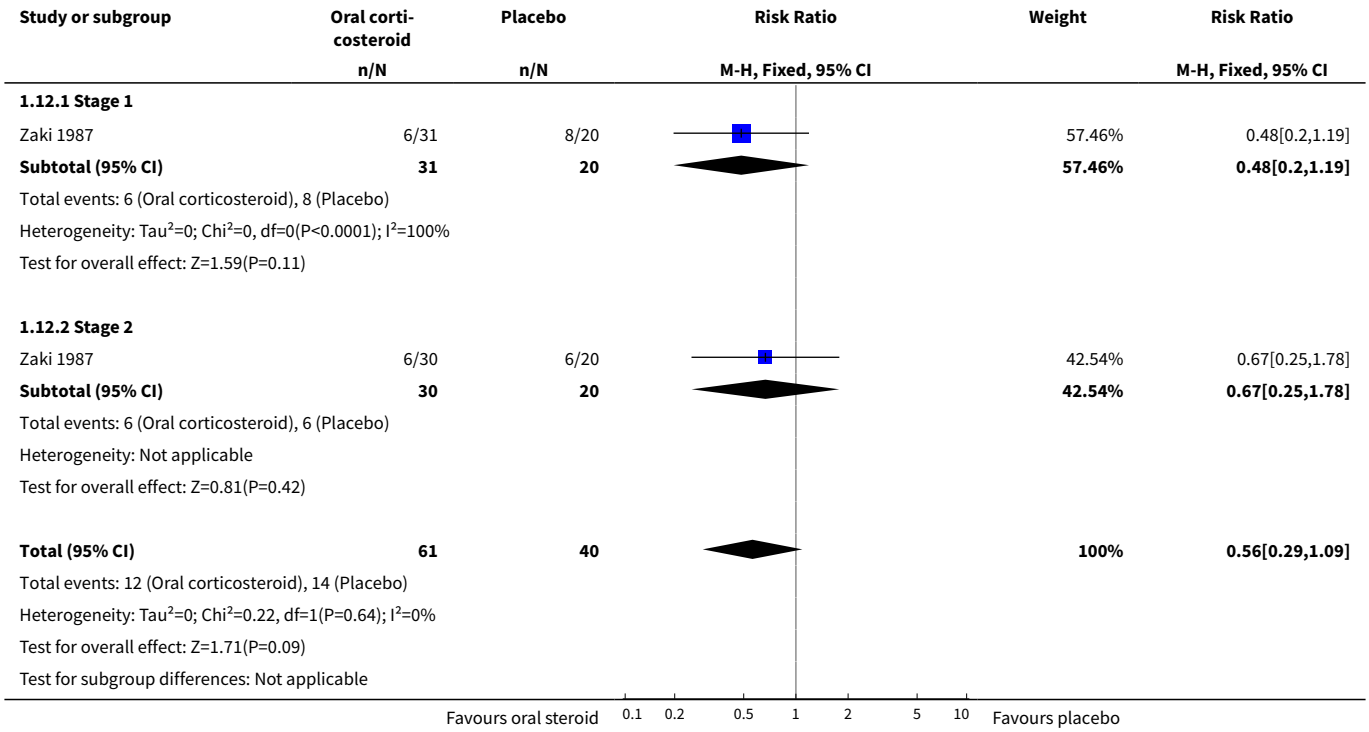


Analysis 1.11. Comparison 1 Oral steroids versus placebo, Outcome 11 FVC (dichotomous data) - unchanged.

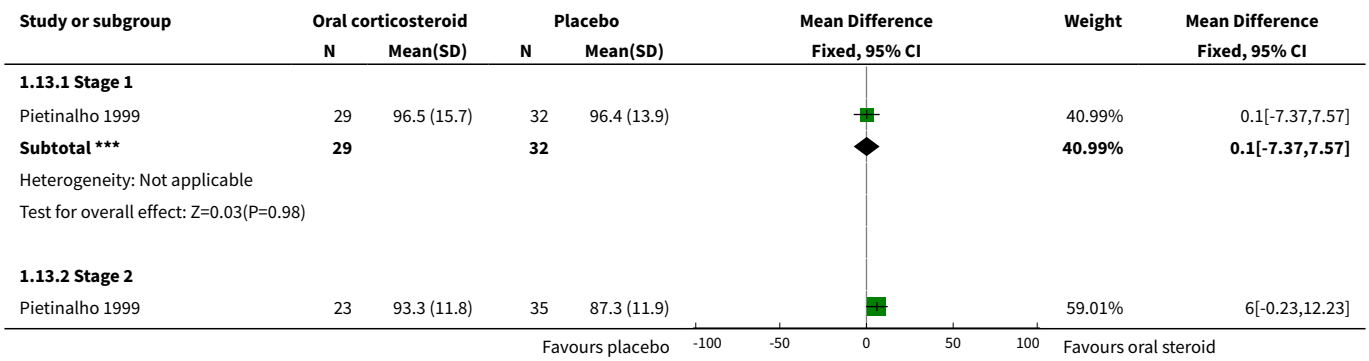


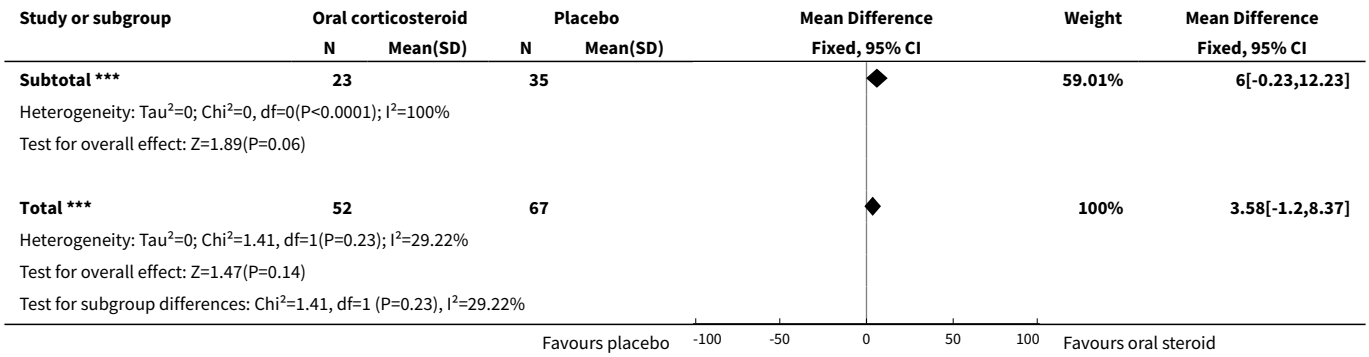


Analysis 1.12. Comparison 1 Oral steroids versus placebo, Outcome 12 FVC (dichotomous data) - worse.

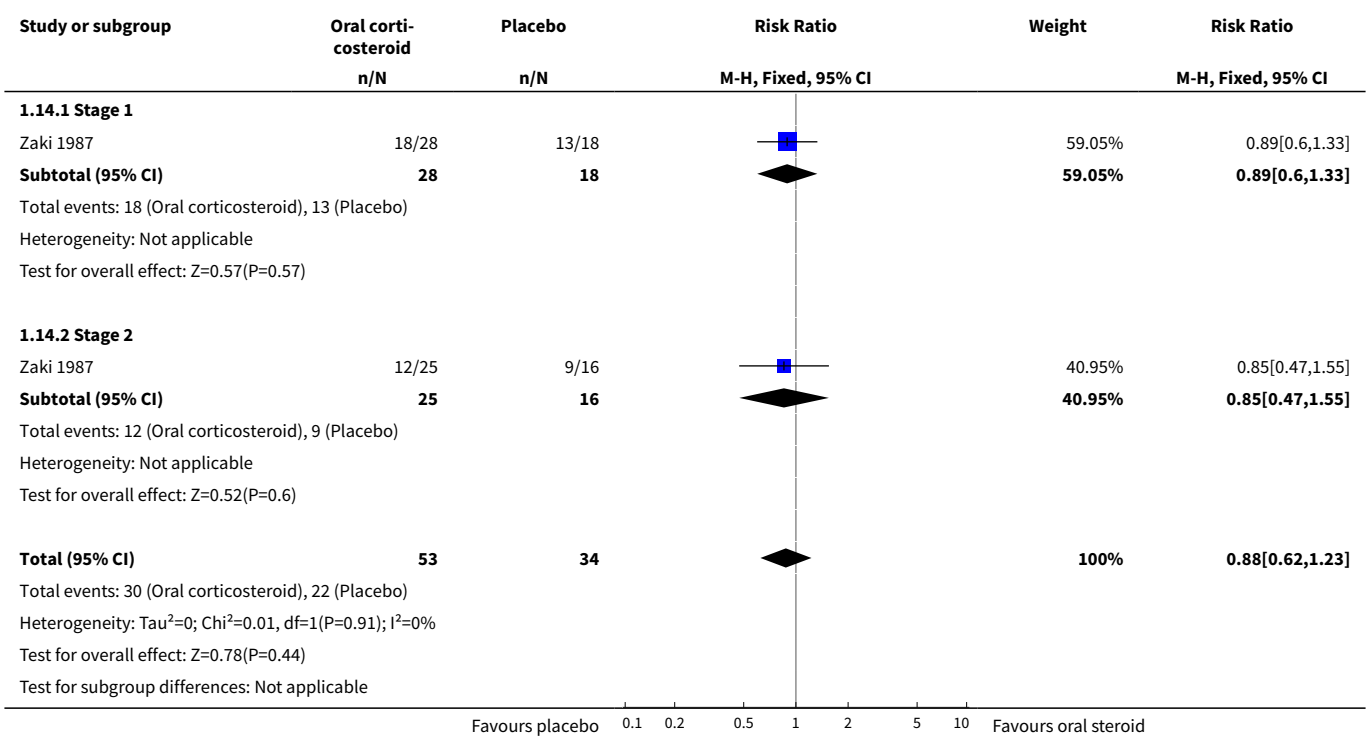


Analysis 1.13. Comparison 1 Oral steroids versus placebo, Outcome 13 FVC (% predicted).

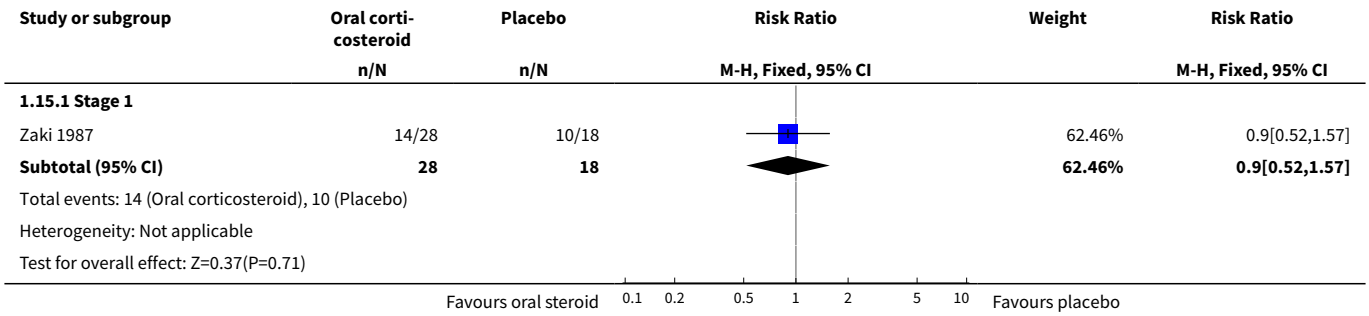


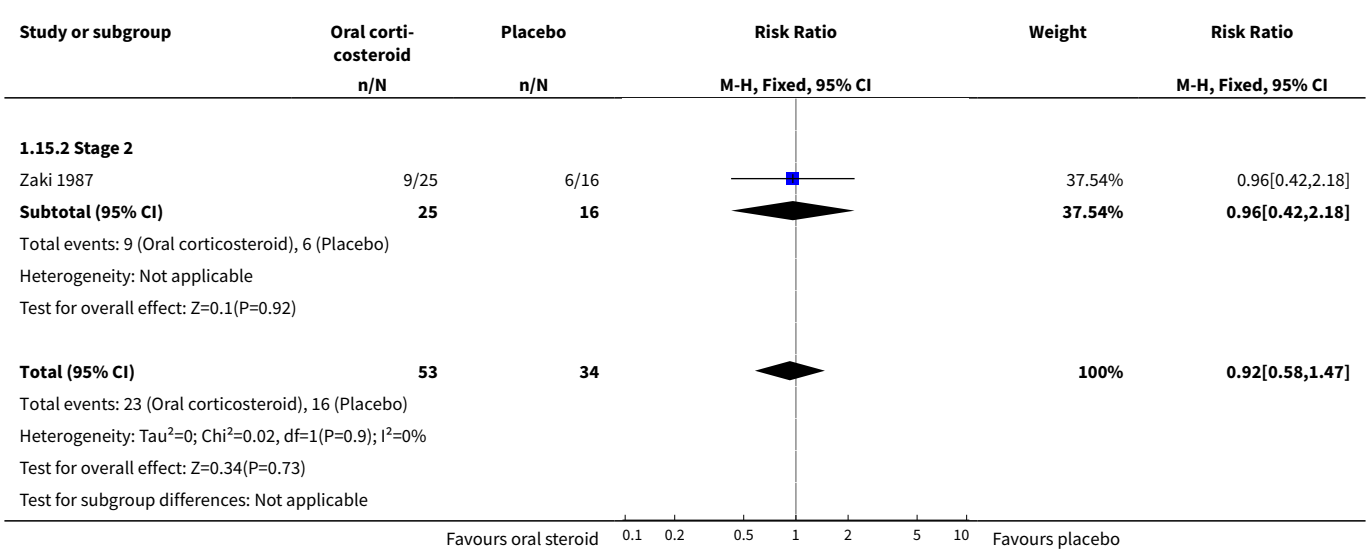


Analysis 1.14. Comparison 1 Oral steroids versus placebo, Outcome 14 DLCO(dichotomous data) - improved.

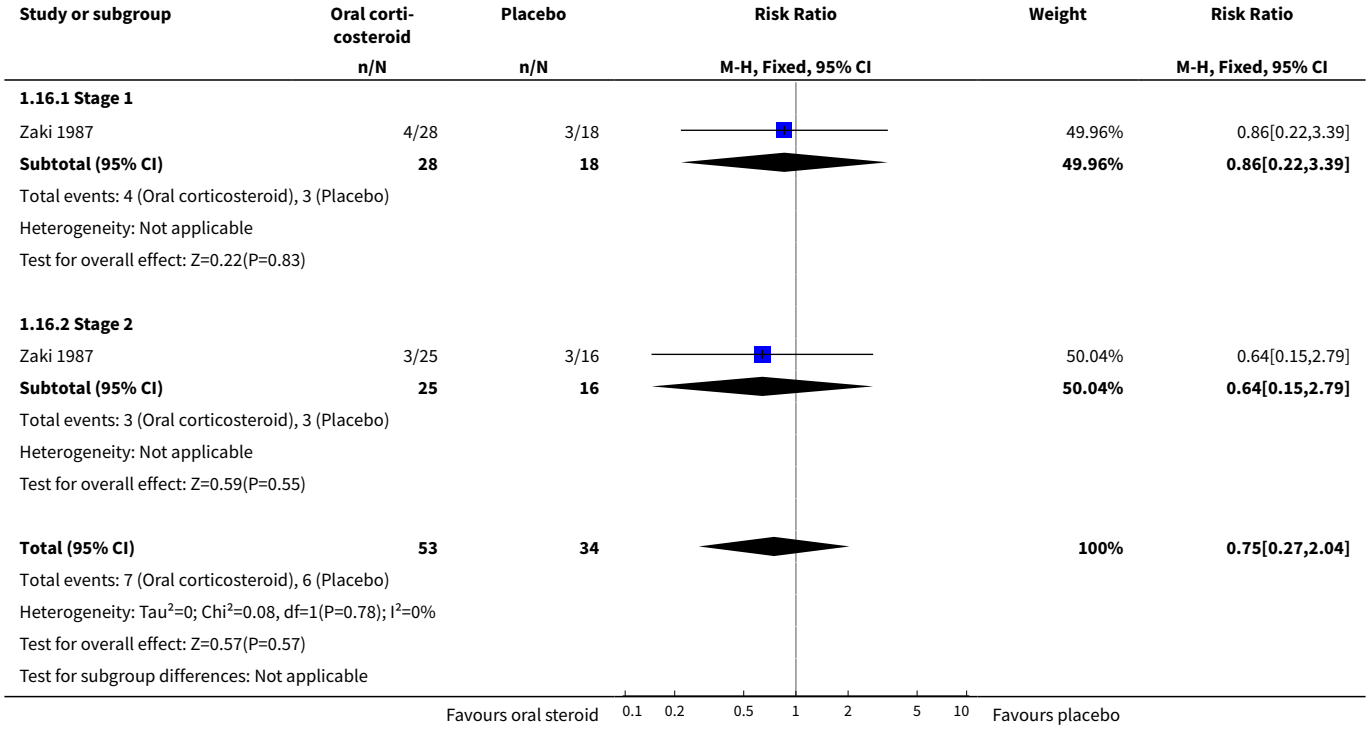


Analysis 1.15. Comparison 1 Oral steroids versus placebo, Outcome 15 DLCO(dichotomous data) - unchanged.

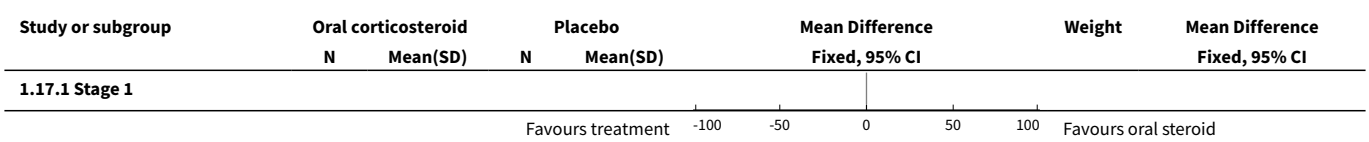


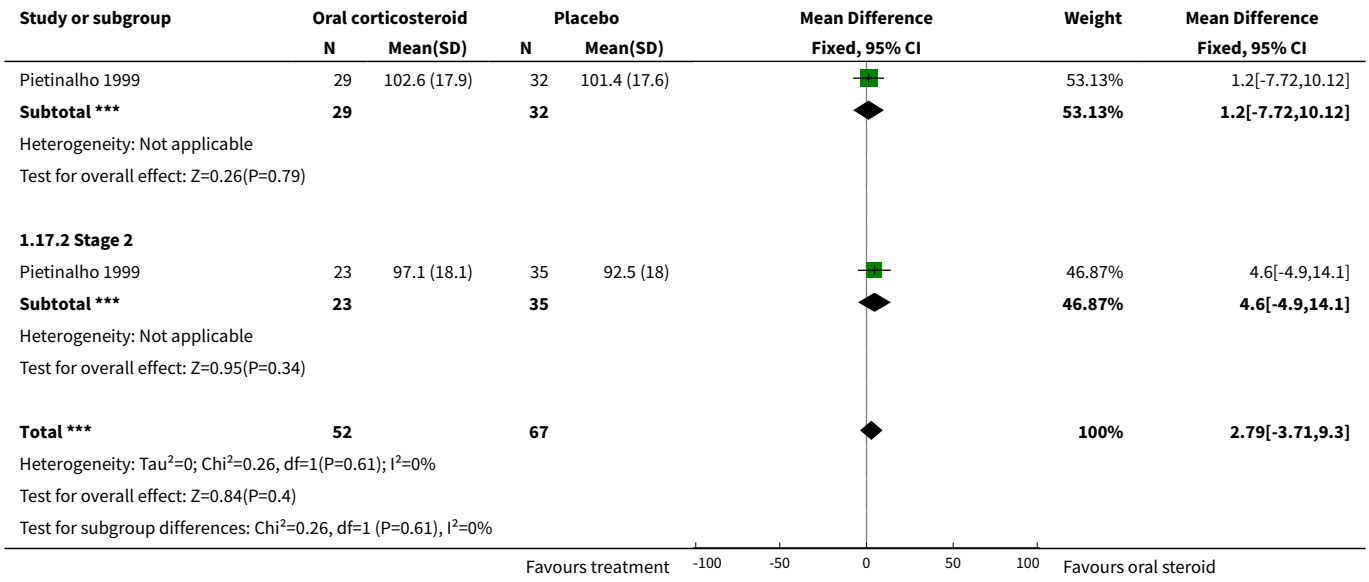


Analysis 1.16. Comparison 1 Oral steroids versus placebo, Outcome 16 DLCO(dichotomous data) - worse.



Analysis 1.17. Comparison 1 Oral steroids versus placebo, Outcome 17 DLCO (% predicted).





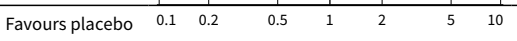
Comparison 2. Inhaled steroids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CXR (improved)	3	60	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.39, 1.62]
1.1 All stages	3	60	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.39, 1.62]
2 CXR (unchanged)	3	60	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.73, 1.88]
2.1 All stages	3	60	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.73, 1.88]
3 CXR (worse)	3	60	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.30, 3.21]
3.1 All stages	3	60	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.30, 3.21]
4 FEV1 predicted (absolute)	3	73	Mean Difference (IV, Fixed, 95% CI)	1.61 [-4.94, 8.16]
4.1 All stages	3	73	Mean Difference (IV, Fixed, 95% CI)	1.61 [-4.94, 8.16]
5 DLCO (%)	2	58	Mean Difference (IV, Fixed, 95% CI)	-2.48 [-11.18, 6.21]
5.1 All stages	2	58	Mean Difference (IV, Fixed, 95% CI)	-2.48 [-11.18, 6.21]
6 DLCO/VA (dichotomous data) - improved by > 15 %	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 All stages	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 DLCO/VA (dichotomous data) - unchanged	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 All stages	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 DLCO/VA (dichotomous data) - worse	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 All stages	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 IVC (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 All stages	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 IVC (Litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 All stages	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Symptoms - improved	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

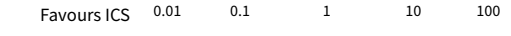
Analysis 2.1. Comparison 2 Inhaled steroids versus placebo, Outcome 1 CXR (improved).

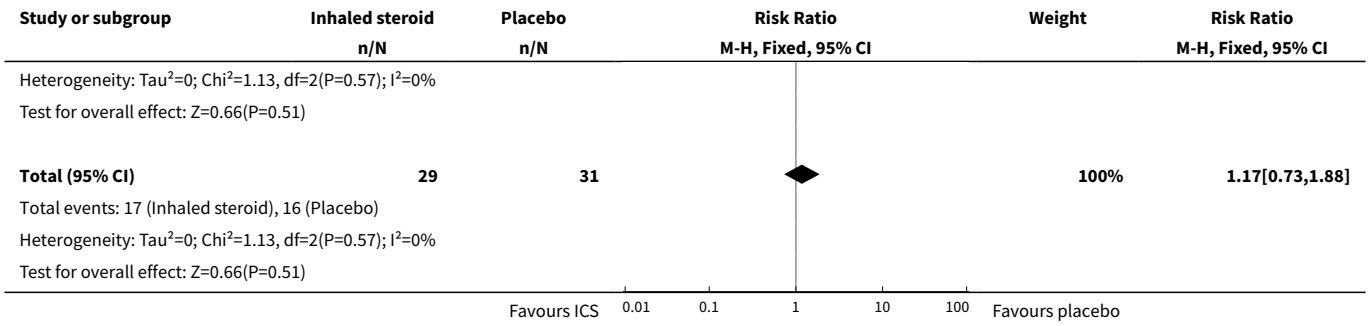
Study or subgroup	Inhaled steroid n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 All stages					
Erkkila 1988	4/8	5/10		41.15%	1[0.39,2.53]
Ludwig 2005	2/6	1/9		7.41%	3[0.34,26.19]
McGrath 2002	2/15	5/12		51.44%	0.32[0.07,1.37]
Subtotal (95% CI)	**29**	**31**		**100%**	**0.8[0.39,1.62]**
Total events: 8 (Inhaled steroid), 11 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.18, df=2(P=0.2); I^2=37.09%					
Test for overall effect: Z=0.62(P=0.53)					
Total (95% CI)	**29**	**31**		**100%**	**0.8[0.39,1.62]**
Total events: 8 (Inhaled steroid), 11 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.18, df=2(P=0.2); I^2=37.09%					
Test for overall effect: Z=0.62(P=0.53)					



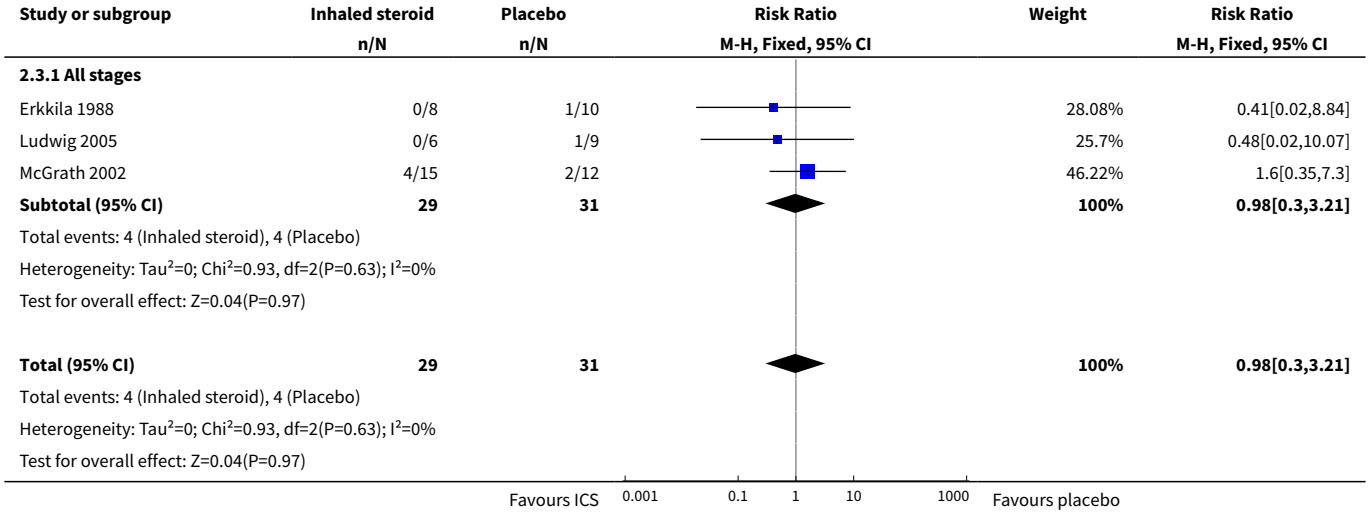
Analysis 2.2. Comparison 2 Inhaled steroids versus placebo, Outcome 2 CXR (unchanged).

Study or subgroup	Inhaled steroid n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 All stages					
Erkkila 1988	4/8	4/10		24.17%	1.25[0.45,3.49]
Ludwig 2005	4/6	7/9		38.07%	0.86[0.44,1.67]
McGrath 2002	9/15	5/12		37.76%	1.44[0.66,3.16]
Subtotal (95% CI)	**29**	**31**		**100%**	**1.17[0.73,1.88]**
Total events: 17 (Inhaled steroid), 16 (Placebo)					

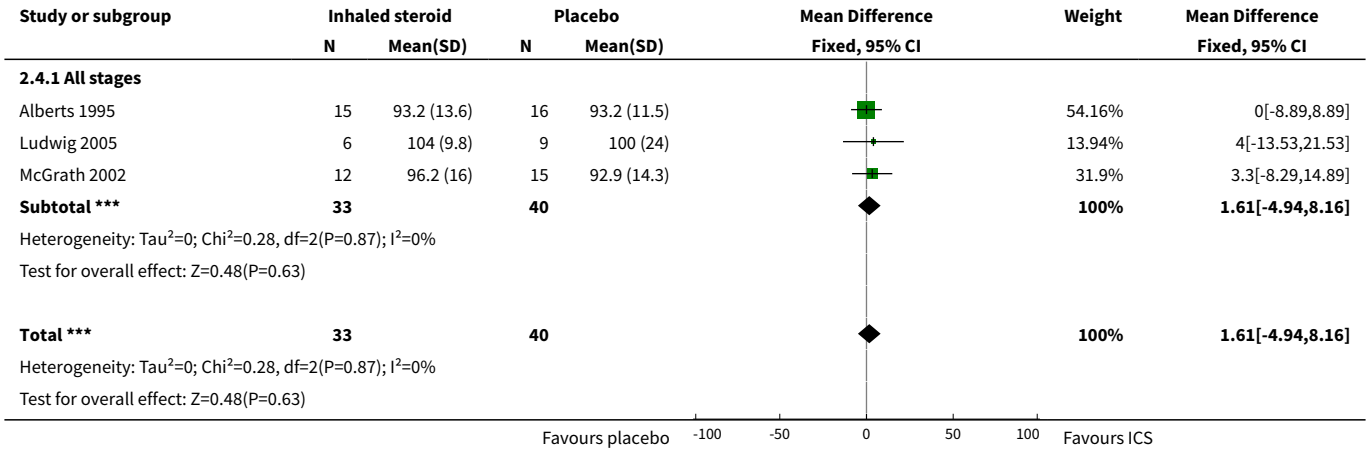




Analysis 2.3. Comparison 2 Inhaled steroids versus placebo, Outcome 3 CXR (worse).

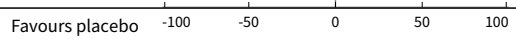


Analysis 2.4. Comparison 2 Inhaled steroids versus placebo, Outcome 4 FEV1 predicted (absolute).



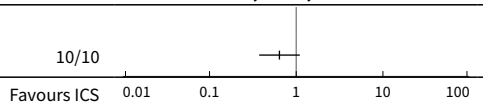
Analysis 2.5. Comparison 2 Inhaled steroids versus placebo, Outcome 5 DLCO (%).

Study or subgroup	Inhaled steroids N	Inhaled steroids Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.5.1 All stages							
Alberts 1995	15	83.3 (13.4)	16	80.5 (17.6)		62.79%	2.8[-8.17,13.77]
McGrath 2002	12	64.5 (18)	15	75.9 (19.7)		37.21%	-11.4[-25.65,2.85]
Subtotal * **	**27**		**31**			**100%**	**-2.48[-11.18,6.21]**
Heterogeneity: Tau^2=0; Chi^2=2.39, df=1(P=0.12); I^2=58.24%							
Test for overall effect: Z=0.56(P=0.58)							
Total * **	**27**		**31**			**100%**	**-2.48[-11.18,6.21]**
Heterogeneity: Tau^2=0; Chi^2=2.39, df=1(P=0.12); I^2=58.24%							
Test for overall effect: Z=0.56(P=0.58)							



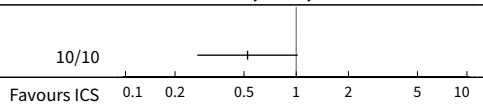
Analysis 2.6. Comparison 2 Inhaled steroids versus placebo, Outcome 6 DLCO/VA (dichotomous data) - improved by > 15 %.

Study or subgroup	Inhaled steroid n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.6.1 All stages				
Erkkila 1988	5/8	10/10		0.64[0.37,1.1]



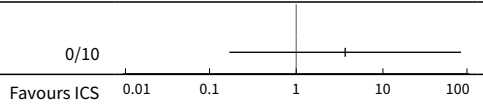
Analysis 2.7. Comparison 2 Inhaled steroids versus placebo, Outcome 7 DLCO/VA (dichotomous data) - unchanged.

Study or subgroup	Inhaled steroids n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.7.1 All stages				
Erkkila 1988	4/8	10/10		0.52[0.27,1.02]



Analysis 2.8. Comparison 2 Inhaled steroids versus placebo, Outcome 8 DLCO/VA (dichotomous data) - worse.

Study or subgroup	Inhaled steroids n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.8.1 All stages				
Erkkila 1988	1/8	0/10		3.67[0.17,79.54]



Analysis 2.9. Comparison 2 Inhaled steroids versus placebo, Outcome 9 IVC (%).

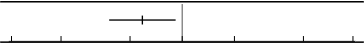
Study or subgroup	Inhaled steroids N	Inhaled steroids Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.9.1 All stages						
Alberts 1995	15	99.3 (16.8)	16	91.4 (11.5)		7.9[-2.3,18.1]

Analysis 2.10. Comparison 2 Inhaled steroids versus placebo, Outcome 10 IVC (Litres).

Study or subgroup	Inhaled steroids N	Inhaled steroids Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.10.1 All stages						
Ludwig 2005	6	5.1 (1.2)	9	4.5 (1.2)		0.61[-0.63,1.85]

Analysis 2.11. Comparison 2 Inhaled steroids versus placebo, Outcome 11 Symptoms - improved.

Study or subgroup	Inhaled steroids n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Alberts 1995	9/16	21/22		0.59[0.38,0.92]

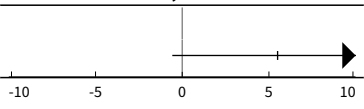


Comparison 3. Oral steroids versus no treatment

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 FVC(continuous)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Stage 2	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 DLCO(continuous data)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Stage 2	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 CXR (normal/im-proved)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Stage 2	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 CXR (unchanged)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Stage 2	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 CXR (worse)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Stage 2	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

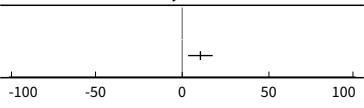
Analysis 3.1. Comparison 3 Oral steroids versus no treatment, Outcome 1 FVC(continuous).

Study or subgroup	Oral steroids N	Oral steroids Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
3.1.1 Stage 2						
Selroos 1979	19	87.9 (9)	18	82.4 (9.8)		5.5[-0.57,11.57]



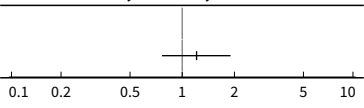
Analysis 3.2. Comparison 3 Oral steroids versus no treatment, Outcome 2 DLCO(continuous data).

Study or subgroup	Oral steroids N	Oral steroids Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
3.2.1 Stage 2						
Selroos 1979	19	85.2 (10.1)	18	74.7 (11.7)		10.5[3.44,17.56]



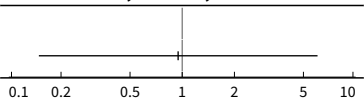
Analysis 3.3. Comparison 3 Oral steroids versus no treatment, Outcome 3 CXR (normal/improved).

Study or subgroup	Oral steroids n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.3.1 Stage 2				
Selroos 1979	14/19	11/18		1.21[0.76,1.9]



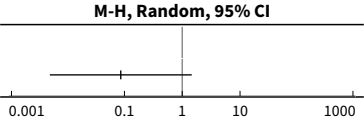
Analysis 3.4. Comparison 3 Oral steroids versus no treatment, Outcome 4 CXR (unchanged).

Study or subgroup	Oral steroids n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.4.1 Stage 2				
Selroos 1979	2/19	2/18		0.95[0.15,6.03]



Analysis 3.5. Comparison 3 Oral steroids versus no treatment, Outcome 5 CXR (worse).

Study or subgroup	Oral steroids n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.5.1 Stage 2				
Selroos 1979	0/19	5/18		0.09[0.01,1.46]



ADDITIONAL TABLES

Table 1. Search history

Year	Search detail
All years to May 2000	References identified: 150
	Unique full text papers retrieved: 25
	Studies meeting inclusion criteria: 9
	Total number of studies included in the review: 9
May 2000 to May 2004	References identified: 926
	Unique full text papers retrieved: 11
	Studies meeting inclusion criteria: 3
	Total number of studies included in the review: 12
May 2004 to May 2006	References identified: 558
	Unique full text papers retrieved: 3
	Studies meeting inclusion criteria: 1
	Total number of studies included in the review: 13
May 2006 to May 2008	References identified: 1123
	Unique full-text papers retrieved: 0
	N meeting inclusion criteria: 0
	Total number of studies included in the review: 13

APPENDICES

Appendix 1. Search strategies: 2008 onwards

MEDLINE*/CENTRAL

1. Lung Diseases, Interstitial/
2. Sarcoidosis, Pulmonary/
3. ((pulmonar$ or respirat$ or lung$) adj3 (sarcoid$ or granuloma$)).mp.
4. Granuloma, Respiratory Tract/
5. or/1-4
6. exp glucocorticoids/
7. exp hydroxycorticosteroids/
8. (steroid$ or corticosteroid$ or glucocorticoid$ or hydroxycorticosteroid$).mp.
9. (budesonide or beclomethasone or fluticasone or triamcinolone or ciclesonide or flunisolide).mp.
10. (prednisone or prednisolone or methylprednisone or dexamethasone or cortisone or hydrocortisone).mp.
11. or/6-10
12. 5 and 11

(*MEDLINE search is combined with the RCT filter outlined in the Airways Group editorial information.)

EMBASE*

1. Sarcoidosis/
2. Interstitial Lung Disease/

3. ((pulmonar$ or respirat$ or lung$) adj3 (sarcoid$ or granuloma$)).mp
4. lung granuloma/ or lung granulomatosis/
5. or/1-4
6. exp corticosteroid/
7. (steroid$ or corticosteroid$ or glucocorticoid$ or hydroxycorticosteroid$).mp
8. (budesonide or beclomethasone or fluticasone or triamcinolone or ciclesonide or flunisolide).mp
9. (prednisone or prednisolone or methylprednisone or dexamethasone or cortisone or hydrocortisone).mp
10. or/6-9
11. 5 and 10

(*EMBASE search is combined with the RCT filter outlined in the Airways Group editorial information.)

Appendix 2. Search strategies 1999-2007

MEDLINE/CENTRAL

1. exp Lung Diseases, Interstitial/
2. (sarcoid$ adj5 pulmonar$).mp.
3. sarcoidosis.mp.
4. alveolitis.mp.
5. (pulmonar$ adj5 fibrosis).mp.
6. (churg-strauss adj3 syndrome$).mp.
7. (wegener$ adj3 granuloma$).mp.
8. pneumonitis.mp.
9. (hemosiderosis adj5 pulmonar$).mp.
10. (granuloma$ adj5 disease$).mp.
11. (interstitial adj5 disease$).mp.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. exp Adrenal Cortex Hormones/
14. (Adrenal cortex hormone$ or steroid$ or corticosteroid$ or glucocorticoid$ or corticoid$).mp.
15. (Hydroxycorticosteroid$ or Corticosterone$ or Hydrocortisone$ or Hydroxycorticosterone$ or Tetrahydrocortisol or Cortisone $ or Cortodoxone$ or Hydroxypregnenolone or Tetrahydrocortisol or Tetrahydrocortisone$ or Pregnenolone$ or Ketosteroid$ or Androstenedione$ or Androsterone$ or Estrone$ or Etiocholanolone$ or Prasterone$ or Dehydroepiandrosterone Sulfate$ or Mineralocorticoid$ or Desoxycorticosterone$ or Hydroxydesoxycorticosterone$).mp.
16. (beclomethasone or beclometasone or beclamet$ or beclocort or becotide or becodisk$ or beclazone or becloforte or Filair or pulvinal or ventide or cyclohaler$ or cyclocap$ or aerobec or asmabec or qvar).mp.
17. (betamethasone or betadexamethasone or flubenisolone or celeston or celestona or celestone or cellestoderm).mp.
18. (Budesonide or cyclohaler$ or cyclocap$ or pulmicort or turbohaler$ or respule$).mp.
19. (fluticasone or flixotide or accuhaler$ or diskhaler$ or evohaler$ or nebule$ or seretide).mp.
20. (dexamethasone or dexsol or decadron).mp.
21. (hydrocortisone or cortisone or efcortisol or Hydrocortone or solu-cortef).mp.
22. (prednisolone or deflacort or calcort or prednisone or methylprednisolone or medrone or solumedrone or depomedrone).mp.
23. (triamcinolone or kenalog).mp.
24. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 12 and 24

EMBASE

1. exp interstitial lung disease/ or exp lung alveolitis/ or exp lung emphysema/ or exp lung fibrosis/
2. exp Lung Sarcoidosis/
3. (sarcoid$ adj5 pulmonar$).mp.
4. sarcoidosis.mp.
5. alveolitis.mp.
6. (pulmonar$ adj5 fibrosis).mp.
7. (churg-strauss adj3 syndrome$).mp.
8. (wegener$ adj3 granuloma$).mp.
9. pneumonitis.mp.
10. (hemosiderosis adj5 pulmonar$).mp.
11. (granuloma$ adj5 disease$).mp.
12. (interstitial adj5 disease$).mp.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. exp Corticosteroid/
15. (Adrenal cortex hormone$ or steroid$ or corticosteroid$ or glucocorticoid$ or corticoid$).mp.

16. (Hydroxycorticosteroid$ or Corticosterone$ or Hydrocortisone$ or Hydroxycorticosterone$ or Tetrahydrocortisol or Cortisone $ or Cortodoxone$ or Hydroxypregnenolone or Tetrahydrocortisol or Tetrahydrocortisone$ or Pregnenolone$ or Ketosteroid$ or Androstenedione$ or Androsterone$ or Estrone$ or Etiocholanolone$ or Prasterone$ or Dehydroepiandrosterone Sulfate$ or Mineralocorticoid$ or Desoxycorticosterone$ or Hydroxydesoxycorticosterone$).mp.
17. (beclomethasone or beclometasone or beclamet$ or beclocort or becotide or becodisk$ or beclazone or becloforte or Filair or pulvinal or ventide or cyclohaler$ or cyclocap$ or aerobec or asmabec or qvar).mp.
18. (betamethasone or betadexamethasone or flubenisolone or celeston or celestona or celestone or cellestoderm).mp.
19. (Budesonide or cyclohaler$ or cyclocap$ or pulmicort or turbohaler$ or respule$).mp.
20. (fluticasone or flixotide or accuhaler$ or diskhaler$ or evohaler$ or nebule$ or seretide).mp.
21. (dexamethasone or dexsol or decadron).mp.
22. (hydrocortisone or cortisone or efcortisol or Hydrocortone or solu-cortef).mp.
23. (prednisolone or deflacort or calcort or prednisone or methylprednisolone or medrone or solumedrone or depomedrone).mp.
24. (triamcinolone or kenalog).mp.
25. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 13 and 25

WHAT'S NEW

Date	Event	Description
24 March 2010	Amended	Spelling mistake corrected

HISTORY

Protocol first published: Issue 1, 1997
Review first published: Issue 1, 1999

Date	Event	Description
23 July 2008	Amended	Converted to new review format.
1 May 2008	New search has been performed	Literature search re-run; no new studies identified.
1 May 2006	New search has been performed	Literature search re-run; one new study met the review eligibility criteria, but this did not alter the conclusions of the review (Ludwig 2005)
28 January 2005	New citation required and conclusions have changed	Five new studies met the inclusion criteria for this update of the review (search results from May 2004). The trials assessed steroid efficacy in these ways: du Bois 2003 and Milman 1994 assessed inhaled steroid versus placebo. Data from these studies could not be utilised as not all participants were steroid-naive at study entry. Pietinalho 1999 contributed data on long-term follow-up. Data from this study had previously been included on short-term treatment effectiveness Baughman 2002 assessed an inhaled steroid as oral steroid tapering agent. This small study did not add new data to the existing analyses. It did not provide definitive evidence on the effectiveness of inhaled steroid therapy in sarcoidosis. McGrath 2002 assessed inhaled steroids versus placebo without an oral steroid tapering protocol. Although data could be pooled

Date	Event	Description
		with one existing study the sample size for this comparison remains very small, and the effect estimate imprecise. Roth 1975 assessed steroid therapy versus no treatment and assessed outcome at long-term follow-up. Study findings from this study should be interpreted with caution due to irregular participant assessment. Overall the conclusions of the review were not altered by the inclusion of these studies. They did however, provide different insights in to the use of steroids in pulmonary sarcoidosis.
3 May 2004	New search has been performed	Literature search re-run

CONTRIBUTIONS OF AUTHORS

Shanthi Paramothayan: protocol initiation, study assessment, data extraction, analysis and interpretation. UPDATE: study assessment, data extraction, analysis and interpretation.

Paul Jones: protocol initiation, study assessment, data extraction, analysis and interpretation

Toby Lasserson: review update - assessment of search results, data extraction, entry and write-up.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

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External sources

- South Thames Research and Training Bursary, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Administration, Oral; Glucocorticoids [*therapeutic use]; Radiography; Randomized Controlled Trials as Topic; Sarcoidosis, Pulmonary [diagnostic imaging] [*drug therapy]

MeSH check words

Humans